NATO

DNA1.940701.021

DNA-TR-81-237

INITIAL HUMAN RESPONSE TO NUCLEAR RADIATION

George H. Anno
Harold L. Brode
Ruth Washton-Brown
Pacific-Sierra Research Corporation
12340 Santa Monica Boulevard
Los Angeles, California 90025

1 April 1982

Technical Report

CONTRACT No. DNA 001-81-C-0067

APPROVED FOR PUBLIC RELEASE;
DISTRIBUTION UNLIMITED.

THIS WORK WAS SPONSORED BY THE DEFENSE NUCLEAR AGENCY
UNDER RDT&E RMSS CODE B310081466 P99QAXDB00025 H2590D.

Prepared for
Director
DEFENSE NUCLEAR AGENCY
Washington, DC 20305

for leukemia. All received preirradiation medical preparation. Dose and associated response times are summarized below:

Dose (rads)	Onset of Nausea and Vomiting after Treatment Began
200	2 hr
750 (effective dose for prodromal effects, 500-625), 375 (@ 25/min) midline to each side of body, 5 min to turn body	25 min
800 (effective dose, 600-650), 200 (@ 14/min) to each of four sides of body	45 min to 1 hr

W. D. Rider and R. Hasselback, "The Symptomatic and Hematological Disturbance Following Total Body Radiation of 300-rad Gamma-Ray Irradiation," lectures presented at McGill University, Montreal, August 1967, in *Guidelines to Radiological Health*, U.S. Public Health Service, Washington, D.C., 1968, pp. 139-144.

Twenty patients were treated with a single 300-rad dose of total-body irradiation. Most patients were children or adolescents suffering from Ewing's tumor of the bone. All were in good general condition, with normal results from peripheral blood and bone marrow studies.

Sudden vomiting began 45 to 60 min after exposure and was not always preceded by nausea. It lasted 15 to 20 min, after which the patients became sleepy. Over the next 6 hr, periods of vomiting alternated with periods of sleep and fatigue, the length of the vomiting periods decreasing while the periods of sleep increased.

Then the patients were asymptomatic until day 25, when they showed some purpura and minor bleeding from the gums. Maximum hemopoietic depression occurred between days 25 and 30. Thereafter, recovery was prompt.

Composite

Composite studies consist of analyses, projections, and information on diagnosis and treatment, based on data from several sources, including accident victims, therapy patients, Japanese atom bomb victims,

begins in week 5 or 6. The course of the illness is a function of the total dose received and individual sensitivity to radiation.

Robert W. Zellmer, "Human Ability to Perform after Acute Sublethal Radiation," *Military Medicine*, Vol. 126, September 1961, pp. 681-687.

Judging from accident, therapy, and Japanese data, the author predicts the performance capability of military personnel after total-body irradiation of ≤600 rads.

Hour 1. All personnel are 100 percent effective. Vomiting, the only limiting factor, should not interfere with assigned duties.

Day 1. Vomiting subsides. Those who received doses of 500 to 600 rads experience general weakness. Combat efficiency should not be impaired more than 20 percent.

Day 2. Hospitalization is required for all personnel who received doses of 500 to 600 rads, 50 percent of those who received 400 rads, and 25 percent of those who received 300 rads. The efficiency of the unhospitalized 400-rad victims is lowered by 50 percent; of the 300-rad victims, 25 percent.

Day 3. Latent phase begins.

Days 14 to 21. Manifest illness begins. Loss of combat efficiency is total among those who received doses of ≥400 rads; 75 percent among those who received 300 rads; and 10 percent among those who received 200 rads.

Expert Opinion

The studies included in this category contain both factual data and judgments by specialists with considerable firsthand experience in human radiobiology.

George E. Thoma, Jr., and Neil Wald, "The Diagnosis and Management of Accidental Radiation Injury," *Journal of Occupational Medicine*, Vol. 1, August 1959, pp. 421-447.

Drawing on clinical records, the authors set forth the case histories of five hypothetical victims of total-body irradiation. Each history suggests the likely response of a healthy person of the indicated age when exposed to the indicated dose.

1. A 27-year-old male exposed to 53 rads shows no clinical or laboratory symptoms that can be attributed to radiation exposure (representative of group I).
2. A 46-year-old male is exposed to 330 rads. Two hours later he becomes nauseated; the nausea persists and he vomits five times in the next 24 hr. He is weak and fatigued for 4.5 days. Over the next several weeks, he develops infection and manifests reduced platelet and leukocyte counts. Weakness and fatigue gradually diminish, and he returns to light work 5 months after the accident (group II).
3. A 37-year-old male is exposed to 718 rads. Within 45 min he becomes nauseated and retches and vomits violently; those symptoms are accompanied by profuse sweating and extreme weakness. Nausea and vomiting continue for the next 12 hr. From days 4 through 13 he is free of symptoms except for weakness, low-grade fever, and excessive sweating. On day 14 his temperature suddenly rises, indicating infection. By day 23 his general condition has deteriorated badly and he is prostrate and disoriented. Diarrhea accompanied by abdominal cramps begins on day 25 and increases until day 28, when he suffers a massive hemorrhage from the lower gastrointestinal tract. Death follows on day 29 (group III).
4. A 31-year-old male is exposed to 954 rads. Thirty minutes later he becomes nauseated and begins retching and vomiting. In the next 4 hr the nausea and vomiting, accompanied by abdominal cramps, increase in frequency and severity. By 16 hr after exposure, however, the victim is free of symptoms except fatigue and a low-grade fever; he remains in this condition for 5 days. On day 7, his temperature rises and nausea and vomiting recur; platelet and leukocyte counts drop. The symptoms intensify, and the victim dies on day 11 (group IV).
5. Within 8 min after being exposed to 7000 rads, a 37-year-old male begins retching violently and is confused and unable to walk. Vomiting and confusion persist, and prostration is marked after 16 hr. After 21 hr, the victim dies (group V).

Herbert B. Gerstner, "Practical Implications of the Initial Reaction to Penetrating Ionizing Radiation," unpublished manuscript, U.S. Air Force School of Aerospace Medicine, 1970.

Clinical experience with therapy patients receiving doses of up to 300 rems suggests that a sizable population exposed to radiation will cluster in three general groups according to the victims' radiation sensitivity: hypersensitive, normosensitive, and hyposensitive. More will be said about this classification in Sec. 3.

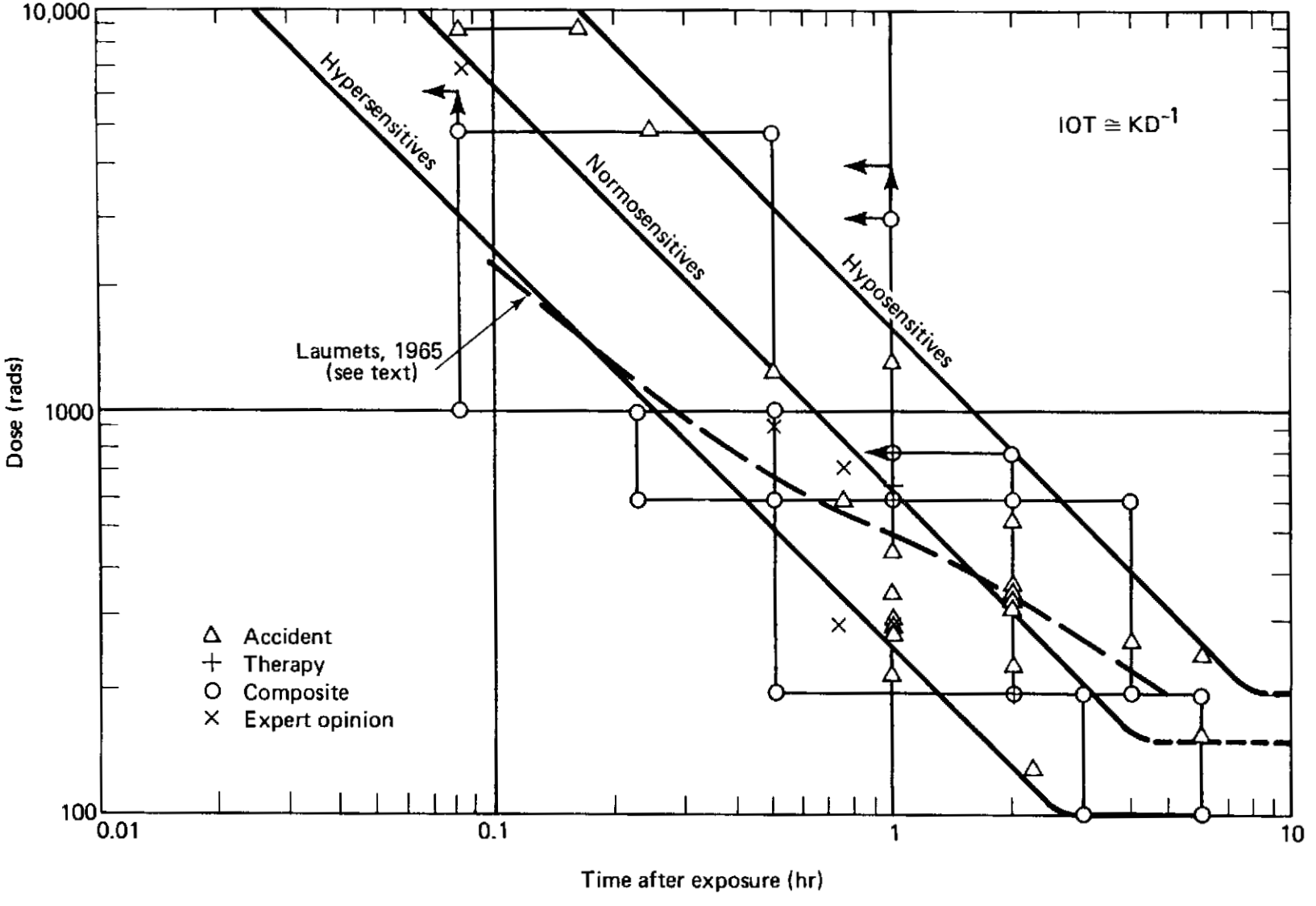


Figure 3. Onset of initial symptoms.

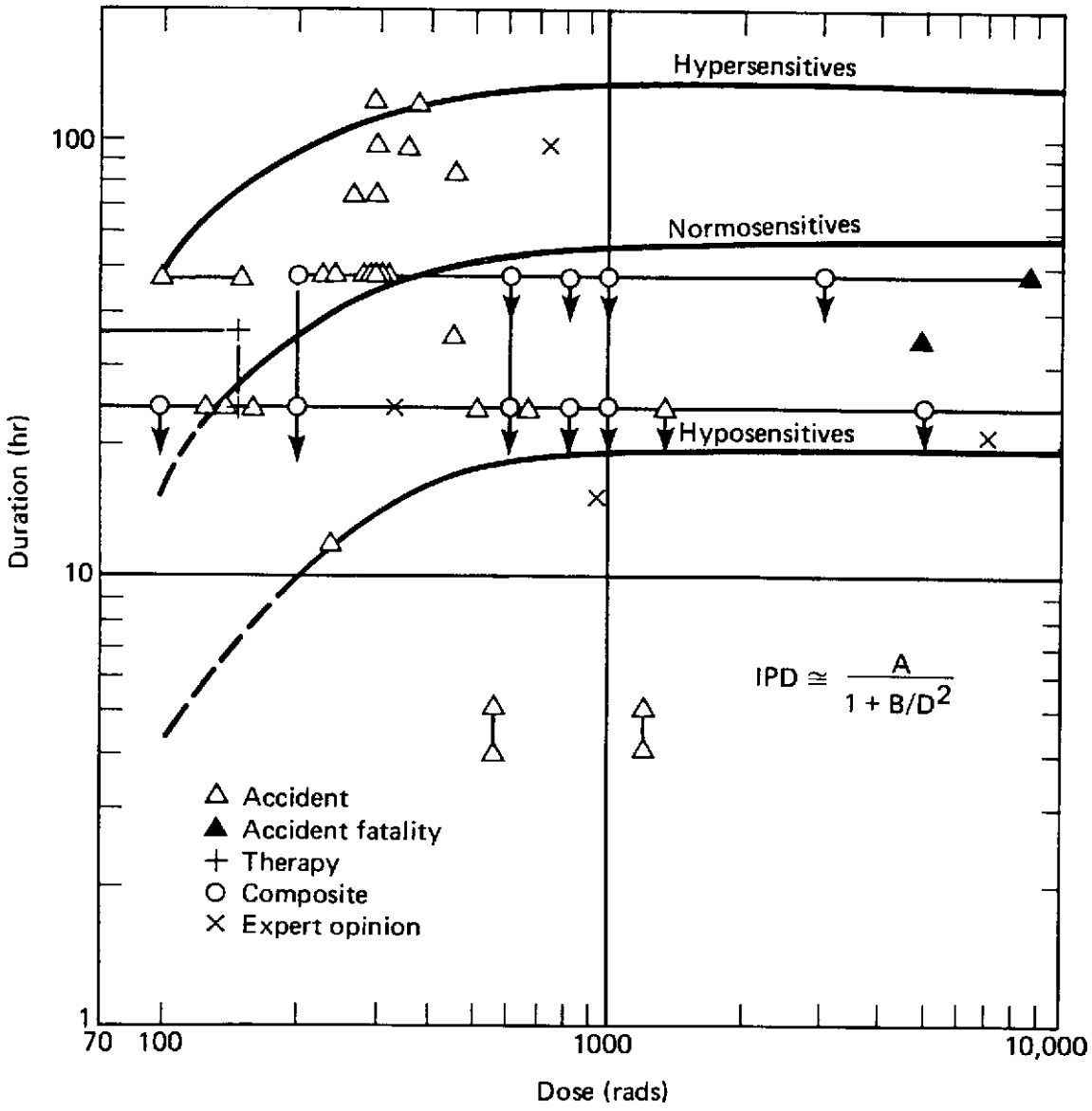


Figure 4. Initial period.

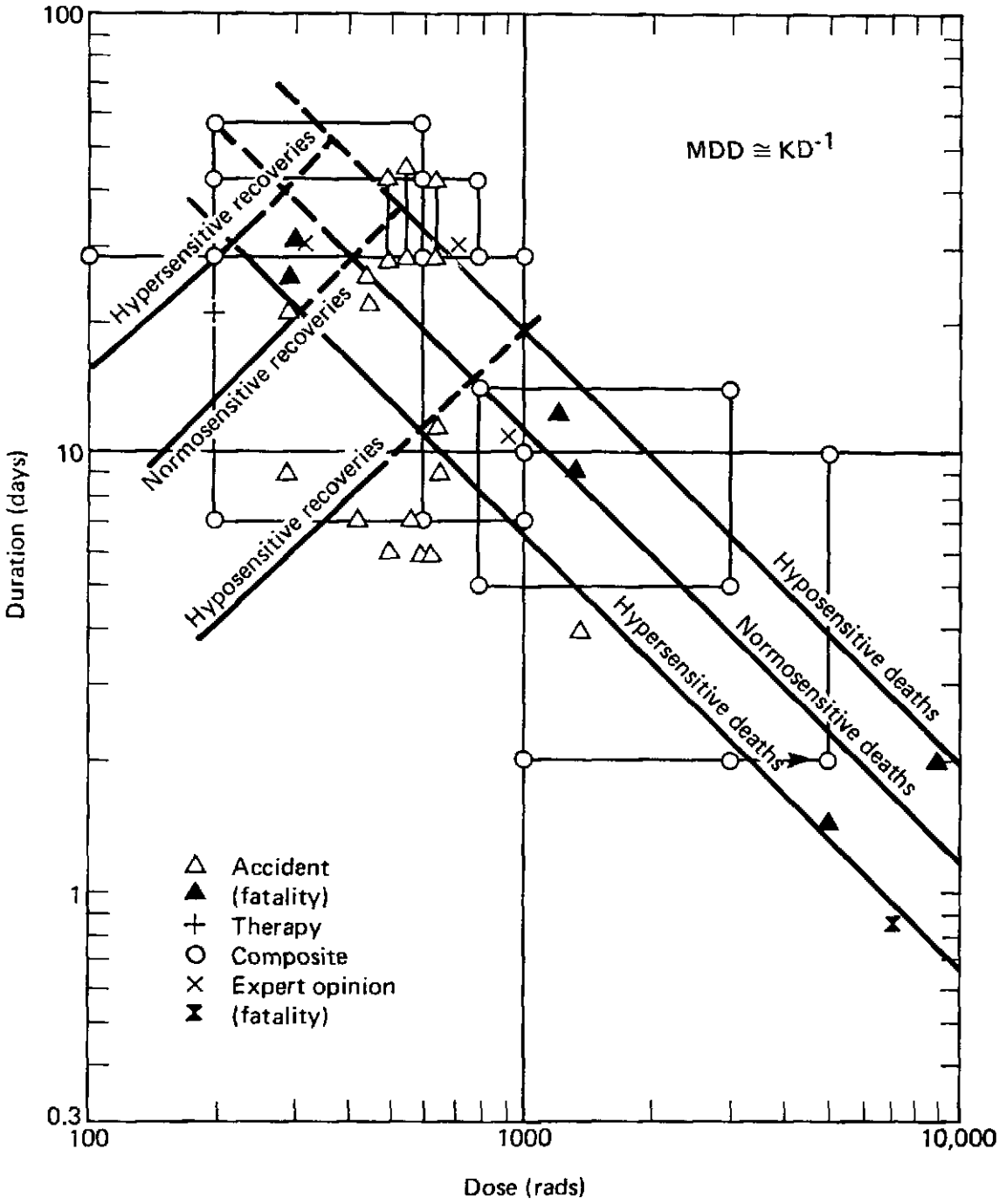


Figure 7. Manifest-illness period for all victims.

t_1 = onset time of initial symptoms (IOT)

T_1 = initial period (IPD)

T_R = latent period (MOT - IOT)

t_2 = onset time of manifest illness (MOT)

$T_{2,r}$ = manifest-illness period ending in recovery (MDR)

$T_{2,d}$ = manifest-illness period ending in death (MDD)

As Fig. 8 shows, the initial period lasting 3 to 48 hr after exposure is followed by a period of remission (T_R) that increases as the

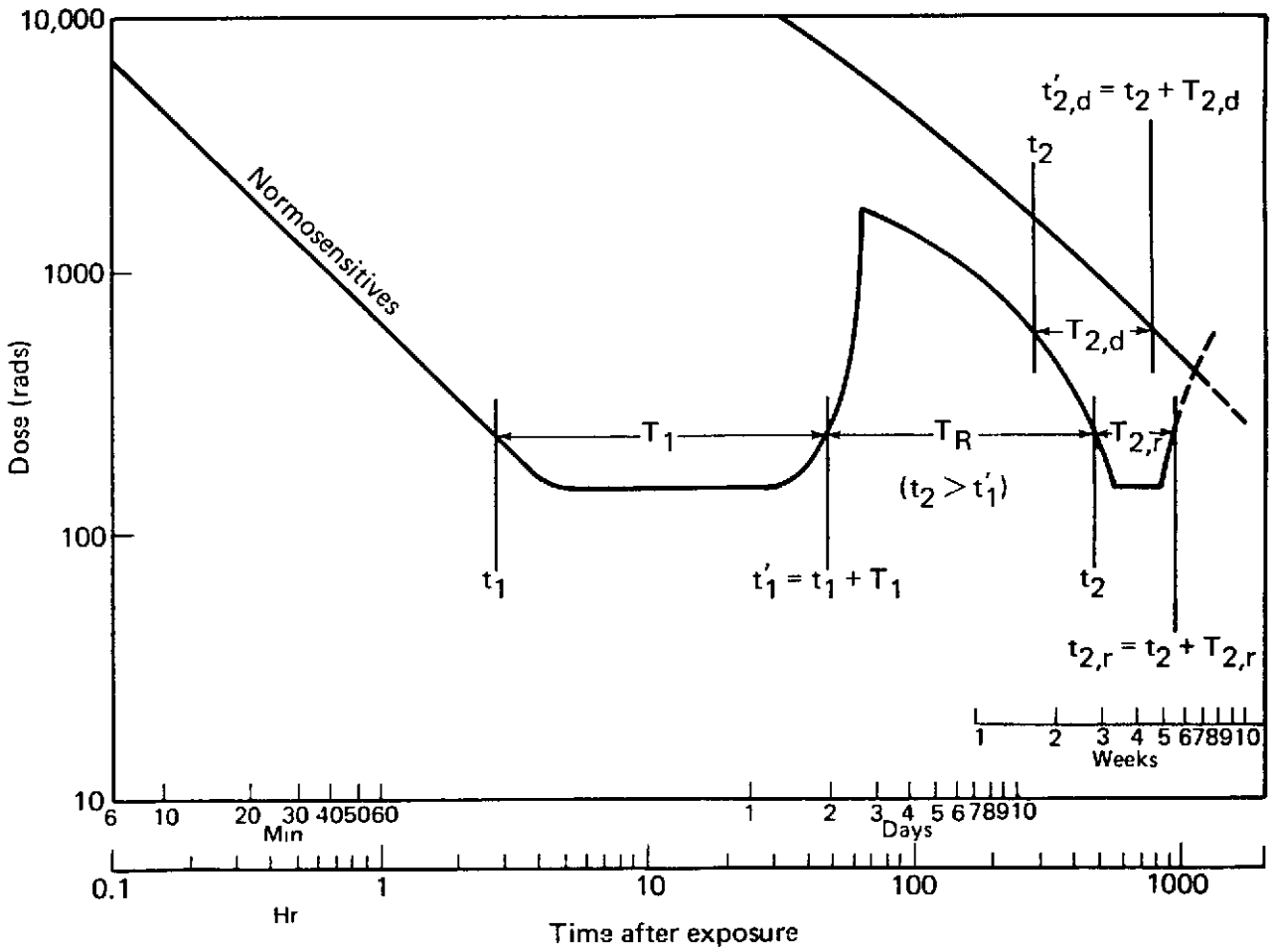


Figure 8. Entire acute radiation response: relation of time and dose for normosensitives.

dose becomes smaller, for doses under 1700 rads. The remission period is formed by the boundaries and intersection of the t_1' and t_2 curves for $t_2 > t_1'$, so its duration is determined indirectly rather than directly from data. The sharp corners in the plot are simply a consequence of combining the individual time relationships; such abrupt discontinuities would not be expected in a thorough statistical analysis.

Figure 9 shows the curves for all three response groups for comparison. There are substantial differences in all times and periods, although the log-log plot somewhat obscures the differences in the times of death and recovery.

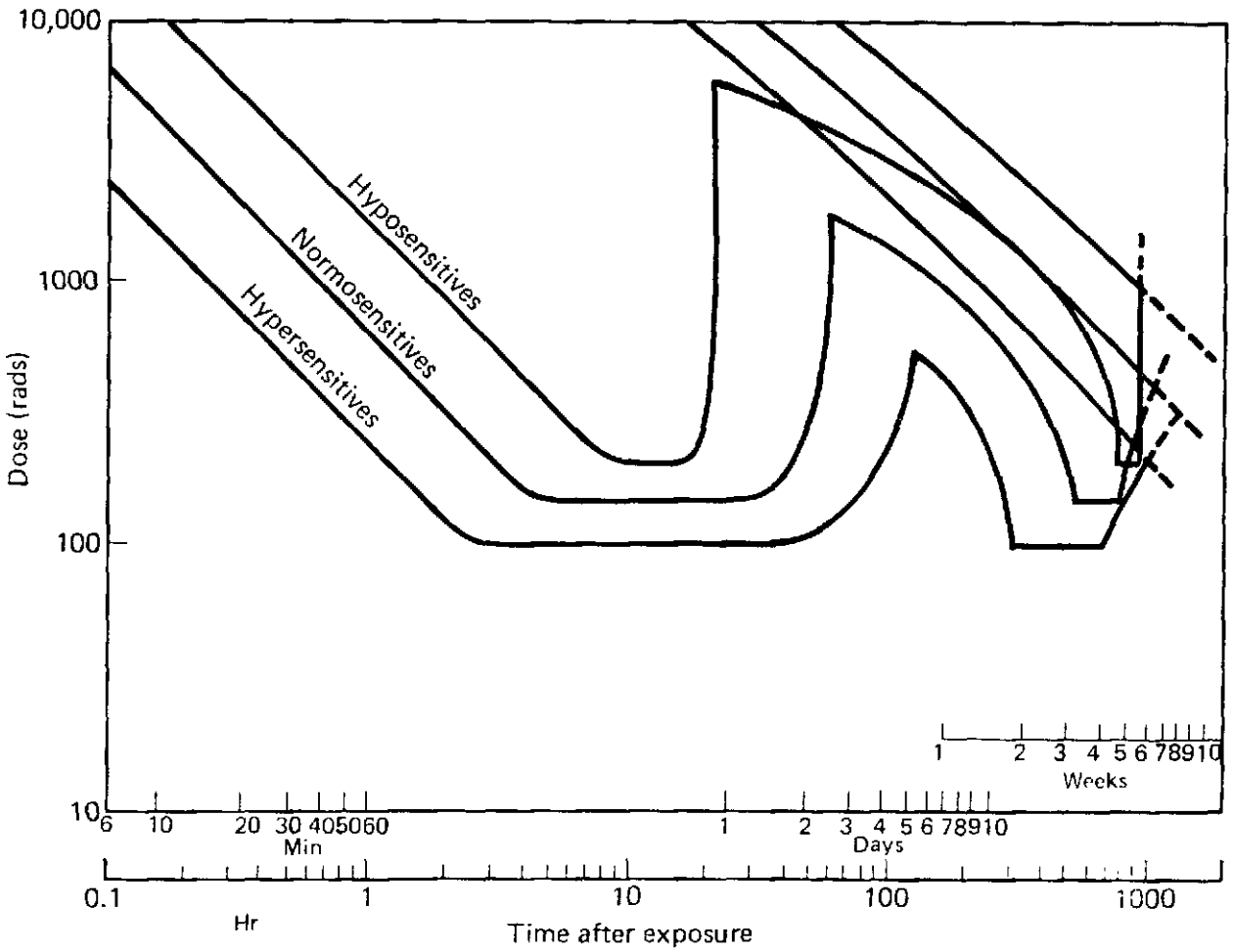


Figure 9. Entire acute radiation response: relation of time and dose for all response groups.

RESPONSE SEVERITY VERSUS TIME

For tactical planning, we need to estimate *how long* after a nuclear attack *how many* military personnel will be able to perform *which* battlefield tasks. It is thus important to link the information presented above on the temporal occurrence of radiation sickness symptoms with the distribution of their severity. The literature provides no specific evidence for a time-severity response profile. It does, however, offer general guidance for developing such a profile for the "typical person" [Gerstner, 1958, 1960], which is depicted in Fig. 10.

The existence of separate prodromal and manifest-illness periods is well supported for doses of more than 100 to several thousand rads [Brown, 1953; Miller et al., 1958; Thoma and Wald, 1959; Wald and Thoma,

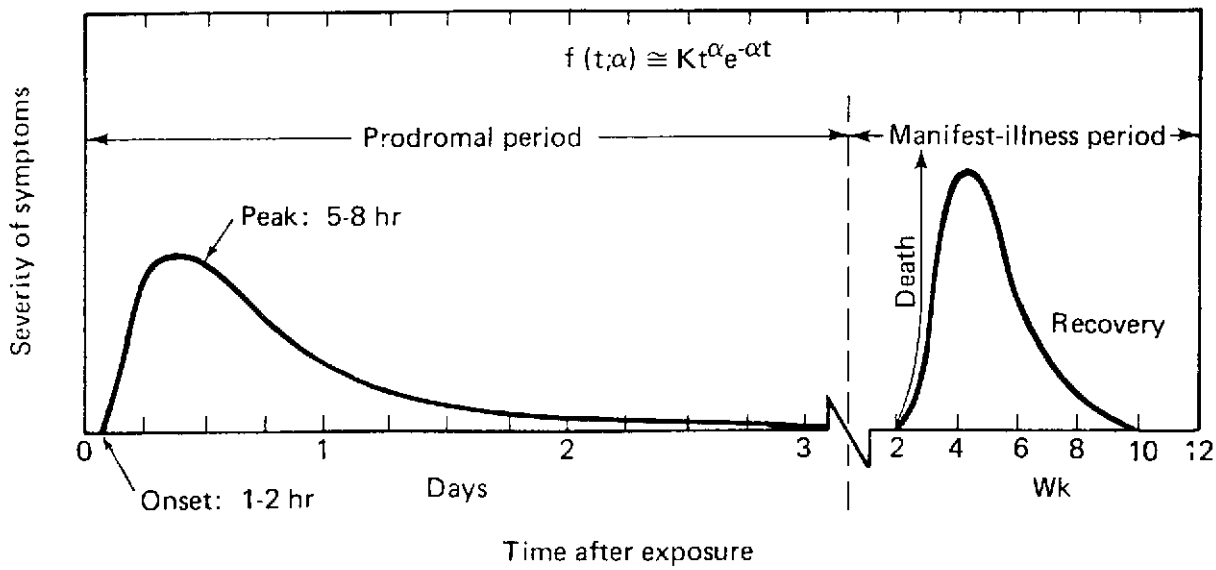


Figure 10. "Typical" (normosensitive) time-severity response profile (dose, ~100 to 400 rads).

1961; and Lushbaugh, 1967, 1969].* At lower doses of ~100 to 400 rads, represented in Fig. 10, prodromal symptoms begin ~1 to 2 hr after exposure, peak 5 to 8 hr postexposure, and subside about 2 to 3 days postexposure.

For low doses (~100 to 135 rads), Miller et al. [1958] place the manifest-illness period at 3 to 4 weeks postexposure, when hemopoietic depression characterized by bleeding, infection, and pancytopenia becomes clinically significant. Based on reactions to therapeutic doses of 300 rads after about 15 min, Rider and Hasselback [1968] estimate the time of maximum hemopoietic depression at 25 to 30 days postexposure. Gerstner's time-severity profiles [1958] resemble those in Fig. 10 in suggesting that symptoms are more severe in the manifest-illness period than in the prodromal period. It is not clear, however, whether Gerstner is comparing a single symptom or the overall illness reflected by a number of symptoms in the two periods.

The profile in Fig. 10 can be conveniently expressed by the relationship

$$f(t;\ \alpha) \cong Kt^{\alpha}\ e^{-\alpha t}\ ,$$

where K is a peak normalizing constant and α is the shape parameter. K adjusts the response amplitude, i.e., percentage of exposed population, and α determines the peak position. Insofar as the peak can shift with dose, α can be shown as a function of dose. Figure 11 illustrates the peak shift. Assuming that initial symptoms subside to 1/10 of their peak value (by an assumed measure) 48 hr after exposure, we estimate a time $t_{1/10}$ of 48 hr for the abatement of symptoms. Figure 11 determines α for the prodromal period depicted in Fig. 10 by selecting the appropriate ratio of $t_{1/10}$ to t_{max}, the time initial symptoms

*However, as noted earlier, the prodromal period may blend into the manifest-illness period for victims exposed to doses greater than 1000 rads. Prodromal symptoms may begin as early as 5 to 15 min postexposure [Lushbaugh, 1969; Langham (ed.), 1967], peak in intensity after about 30 min, and persist for several days, gradually merging with a fatal vascular or gastrointestinal syndrome.

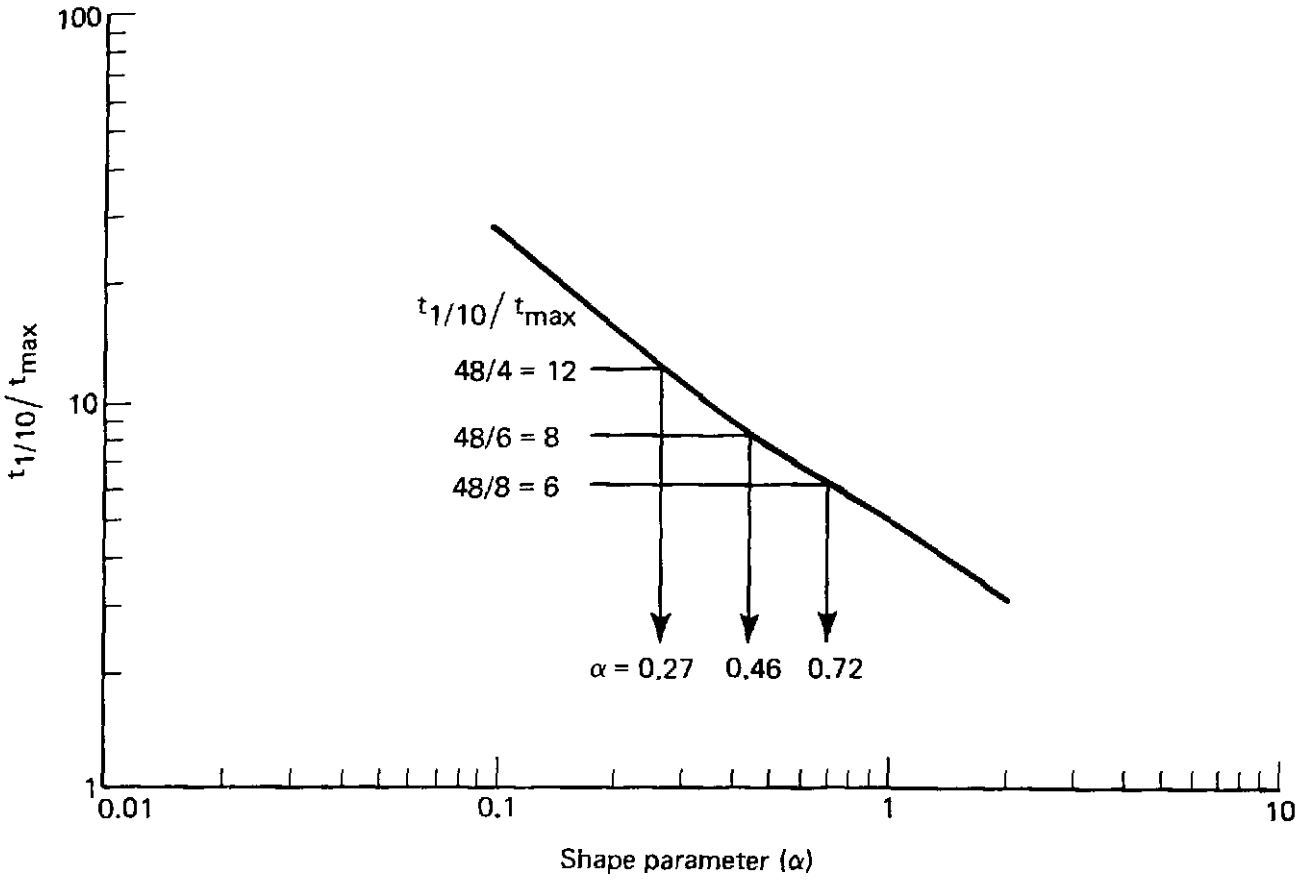


Figure 11. Shape parameter for peaking and abatement of symptoms.

peak. For illustration, three different t_{max} values are assumed (reflecting three doses): 4, 6, and 8 hr. A time-intensity response profile can be similarly developed for the manifest-illness period.

Figure 12 adds the dimension of symptom severity to the dose and time relationships plotted earlier. The shaded areas indicate the onset, peak, and abatement of symptoms in the prodromal and manifest-illness periods. The wide shaded area at the highest doses depicts the profile for victims whose prodromal period merges into a fatal manifest-illness period.

To summarize the results of this section so far, Fig. 13 shows a contour plot of the normosensitive response to radiation relating dose, time, and symptom severity. Here symptom severity refers to the

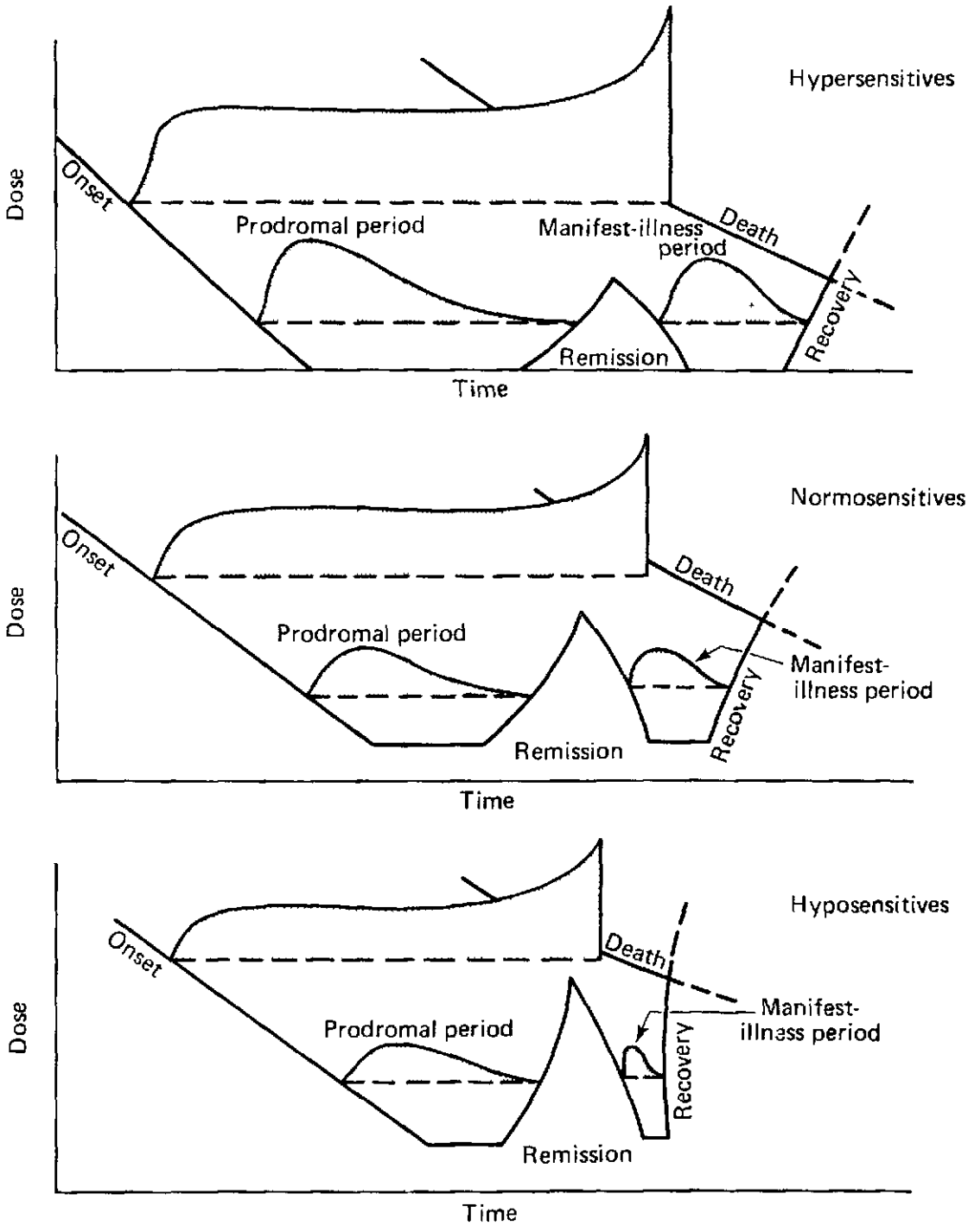


Figure 12. Acute radiation response for all groups: dose-time-severity profile.

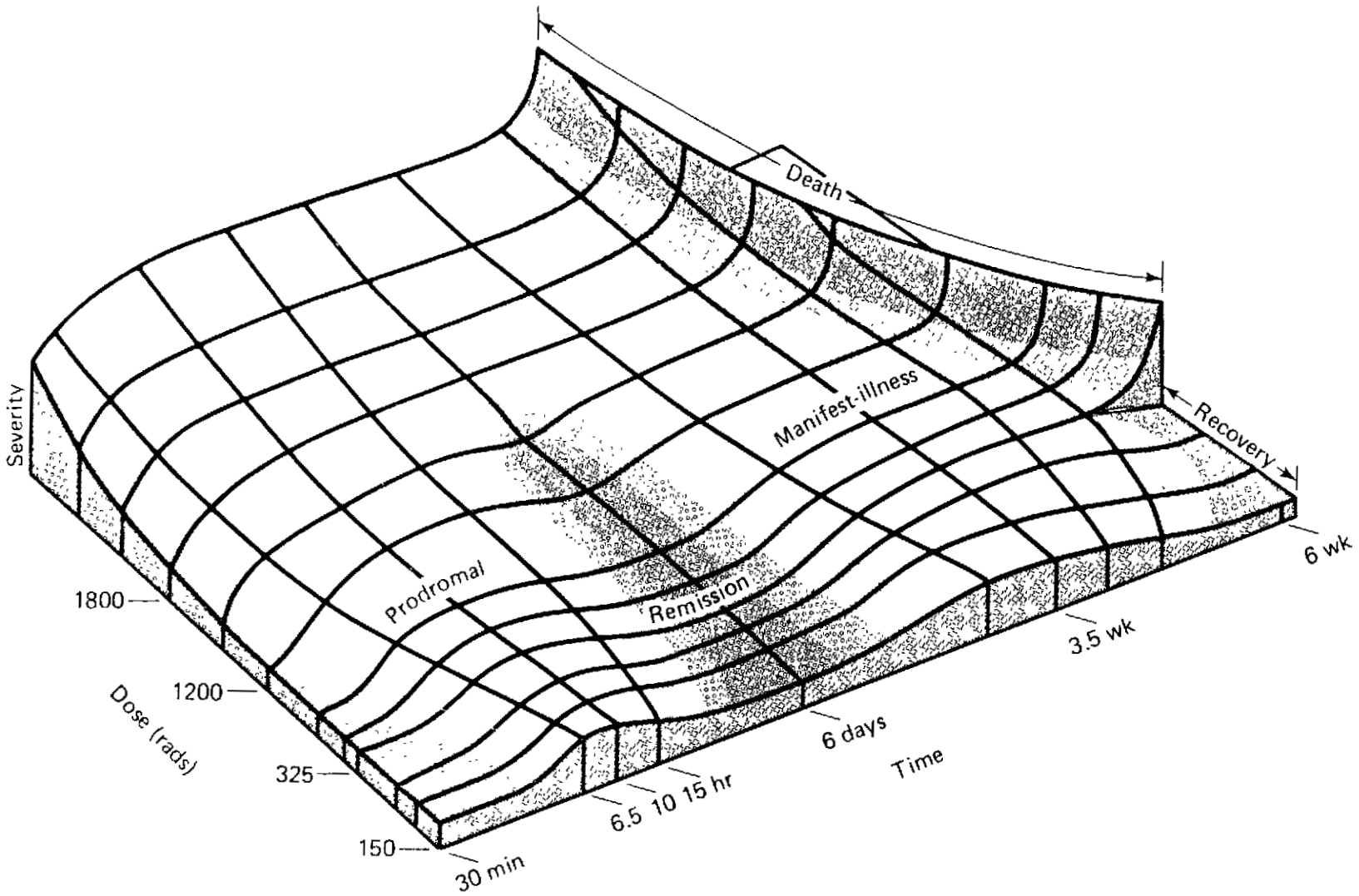


Figure 13. Acute radiation response for normosensitives: contour plot of dose, time, and symptom severity.

combination of symptoms reflecting radiation sickness, not a single symptom. Analogous contours could be developed for particular symptoms or syndromes such as nausea, vomiting, fatigue, diarrhea, and hemopoietic depression, as described by Brucer (comp.) [1959]. The ultimate goal, of course, is to develop a set of contours to project performance impairment for a given radiation dose.

POPULATION RESPONSE

We now consider the prodromal response in a large population exposed to varying doses of ionizing radiation. Figure 14 plots, by dose, rough percentages of the population who might (1) experience nausea and vomiting and (2) fall in each response group classified by severity of symptoms. For a given dose, the component response groups add up to the total population (100 percent). The curves are only suggestive; the lack of data, especially for doses above a few hundred rads, makes anything approaching statistical significance impossible.*

Based on a study of 100 cases (93 therapy patients and 7 accident victims), Lushbaugh et al. [1967] relate clinical responses to TBI doses in a probit analysis of effective doses needed to produce gastrointestinal and other systemic responses. They develop probit relationships for anorexia, nausea, vomiting, fatigue, diarrhea, and death--two sets each, assuming normal and log-normal distributions of the data. We used the relationships for nausea and vomiting assuming a normal distribution:

$$\text{Nausea:} \quad p(D) = 0.008D + 3.837 \ ,$$

$$\text{Vomiting:} \quad p(D) = 0.008D + 3.588 \ ,$$

where D is the dose in rads and the numbers represent probit units. Obtaining cumulative distributions with the logistic formula

*The contents of Fig. 14 and our discussion rely heavily on Gerstner [1958, 1960, 1970], Lushbaugh et al. [1967], Lushbaugh [1969], Langham et al. [1965], and Langham (ed.) [1967].

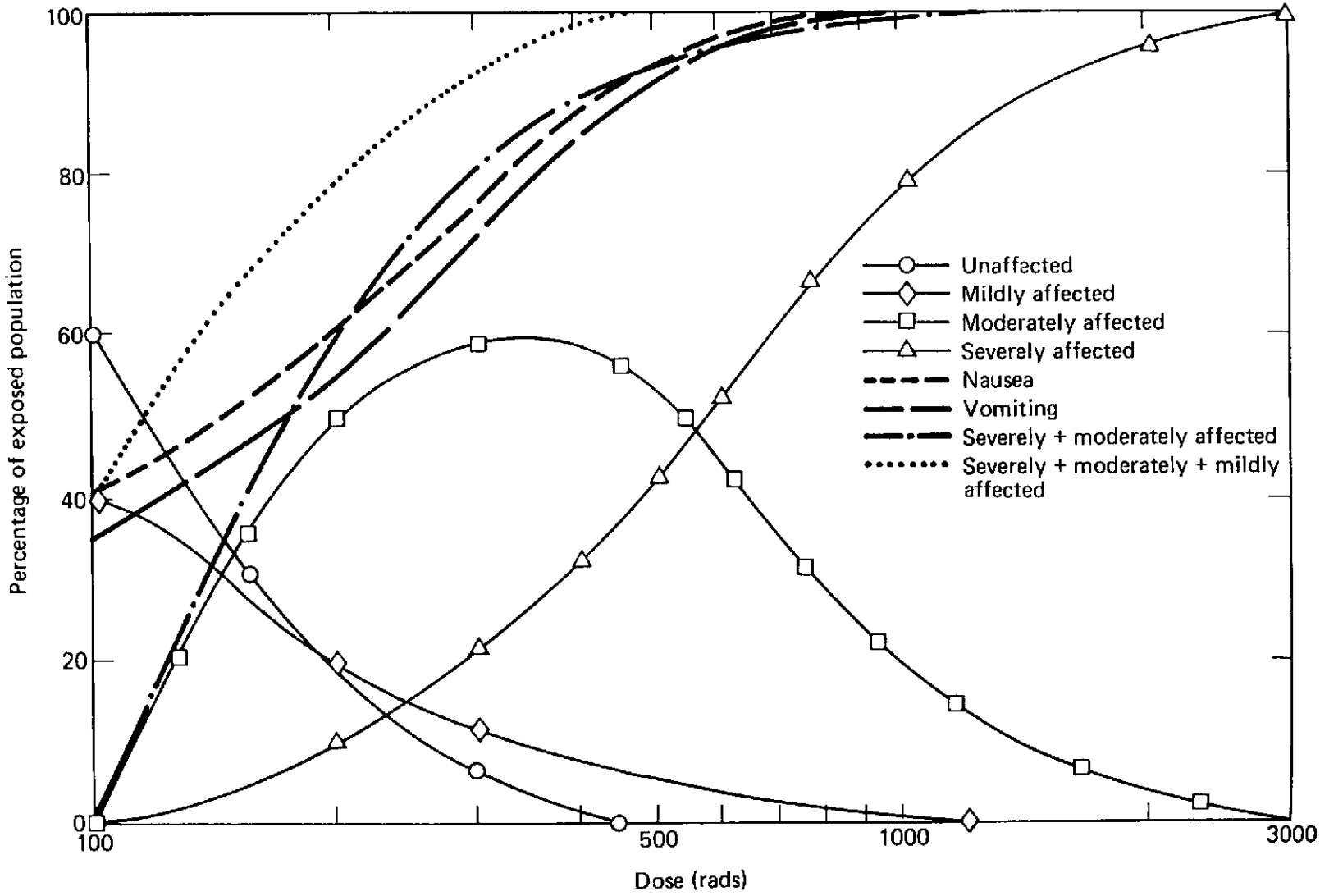


Figure 14. Distribution of radiation response in an exposed population.

$$p(D) = \frac{1}{1 + \exp\{-[p(D) - 5]\}},$$

we plotted the curves for nausea and vomiting in Fig. 14. The p(D) function is of a sigmoid form and nearly indistinguishable from a cumulative normal distribution [Kruskal and Tanure (eds.), 1978]. For a dose of 100 rads, the cumulative values for nausea and vomiting are 41 and 35 percent, respectively; the corresponding values assuming a log-normal distribution--49 and 42 percent for nausea and vomiting, respectively--do not differ greatly, considering the imprecision of the data.

Gerstner [1960] estimates that about 50 percent of the exposed population would be affected by a midline absorbed dose of ~100 rads. Since he is judging from the experience of therapy patients, who were already ill, we think that estimate is slightly high for the general population. We estimate that 40 percent of the population would be affected at 100 rads. At that dose Fig. 14 classifies all responses as mild, so the remaining 60 percent of the population would be unaffected. The peaking of the mild response curve at about 100 rads cannot be specifically verified. However, Gerstner asserts that close to the threshold dose of 70 rads* the initial reaction, if any, takes the mild form of brief spells of fatigue, anorexia, and nausea. Glasstone and Dolan [1977] also doubt that clear-cut prodromal reactions would show up in a population exposed to less than around 70 rads.

In the dose rate of 130 to 200 rads, Gerstner [1960] uses therapy data to estimate the following response pattern: unaffected, 20 percent; mildly affected, 20 percent; moderately affected, 50 percent; and severely affected, 10 percent [Miller et al., 1958; Levin et al., 1959]. Figure 14 reflects that distribution pattern at a dose of 200 rads. Gerstner further asserts, drawing on Brucer (comp.) [1958] and Miller et al. [1959], that the response pattern persists at higher doses,

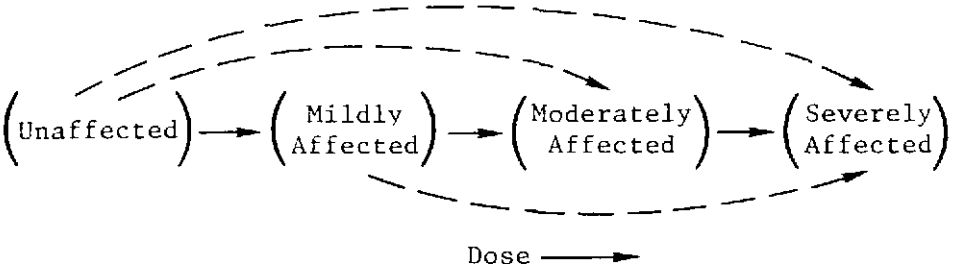
*This and similar dose figures are not precise but are the midline dose equivalents of round-number free-in-air doses.

perhaps up to 540 rads: each person displays the severity of reaction peculiar to his response group.

Later, however, Gerstner [1970] proposes a different response pattern in which hyposensitives (~20 percent of the exposed population) experience the severest symptoms after doses of about 350 rads; normosensitives (60 percent of the population) experience the severest symptoms after about 340 rads; and hypersensitives (20 percent) experience full severity after about 300 rads. Gerstner's suggestion of an apparent plateau in response severity above doses of 300 to 350 rads is not specifically supported by the rest of the literature we examined. On the contrary, the popular view is that severity increases with dose until a point of total incapacitation at doses of several hundred to a few thousand rads [Shelberg and Ulberg, 1967; Glasstone and Dolan, 1977; NCRP, 1974]. In the dose range of 1000 to 10,000 rads, it is difficult to infer any precise trend regarding symptom severity from the data, primarily accident data [Hemplemann et al., 1952; Thoma and Wald, 1959; Karas and Stanbury, 1965; Fanger and Lushbaugh, 1967; Lushbaugh, 1969; Hubner and Fry (eds.), 1980]. The recent study by Cairnie and Robitaille [1980] points out the same difficulty.

Although Gerstner himself did not make the connection [1970], the response pattern in Fig. 14 is consistent with Gerstner's percentages for hypo-, hyper-, and normosensitives above if we assume that at doses of 300 to 350 rads, hyposensitives include both the unaffected and mildly affected, the normosensitives include the moderately affected, and the hypersensitives include the severely affected.

Figure 14 shows that the percentages of unaffected, mildly affected, and moderately affected drop above a certain dose, while the percentage of severely affected rises correspondingly. Over the 100 to 350 rad range, the percentage of the moderately affected rises. The pattern thus presumes that individuals in an exposed population shift to increasingly severe response categories with dose, as illustrated below:



Again, no precise empirical evidence exists to verify the sequence above, let alone the sequence related to dose. However, it seems reasonable that above a certain dose (here assumed to be 3000 rads) essentially all persons in an exposed population will be severely affected by radiation, regardless of their sensitivity classification (hypo-, hyper-, normosensitive).

The response distribution at the highest doses in Fig. 14 seems to be borne out by specific accident accounts. A victim exposed to 1200 rads [Hubner and Fry, 1980: 91-104] showed more than a mild response [Hemplemann et al., 1952], as did two others who received doses of 4500 rads [Fanger and Lushbaugh, 1967] and 8800 rads [Karas and Stanbury, 1965]. Assigning a specific sensitivity classification to any of those victims is of course impossible.

The combined plot for severely and moderately affected in Fig. 14 resembles plots for nausea and vomiting in Lushbaugh et al. [1967]. Thus we surmise that the mildly affected would probably experience nausea but not severe vomiting.

INDIVIDUAL-POPULATION RESPONSE MODEL

Here we attempt to link the individual responses described above for hyper-, normo-, and hyposensitives with the population responses described for the unaffected through severely affected groups. A heuristic approach is necessary to compensate for deficiencies in the empirical data. The dimensions of dose and symptom severity are related only for the initial period as a whole; the variable time dimension is omitted because of insufficient data.

Earlier in this section we postulated the dosages at which each sensitivity group begins to respond to radiation: hypersensitives, 100 rads (dose D_1); normosensitives, 150 rads (D_2); and hyposensitives, 200 rads (D_3). Figure 15 extends the responses presented earlier for individuals in those groups, expressing each group's response in terms of the percentage of incapacitation as a function of dose above the threshold. Each curve depicts a cumulative increase, reaching total incapacitation at doses D_1', D_2', and D_3' for hyper-, normo-, and hyposensitives, respectively. The exact form of the cumulative function is unknown; variations in response for each sensitivity group might be normally or log-normally distributed with respect to dose. Moreover,

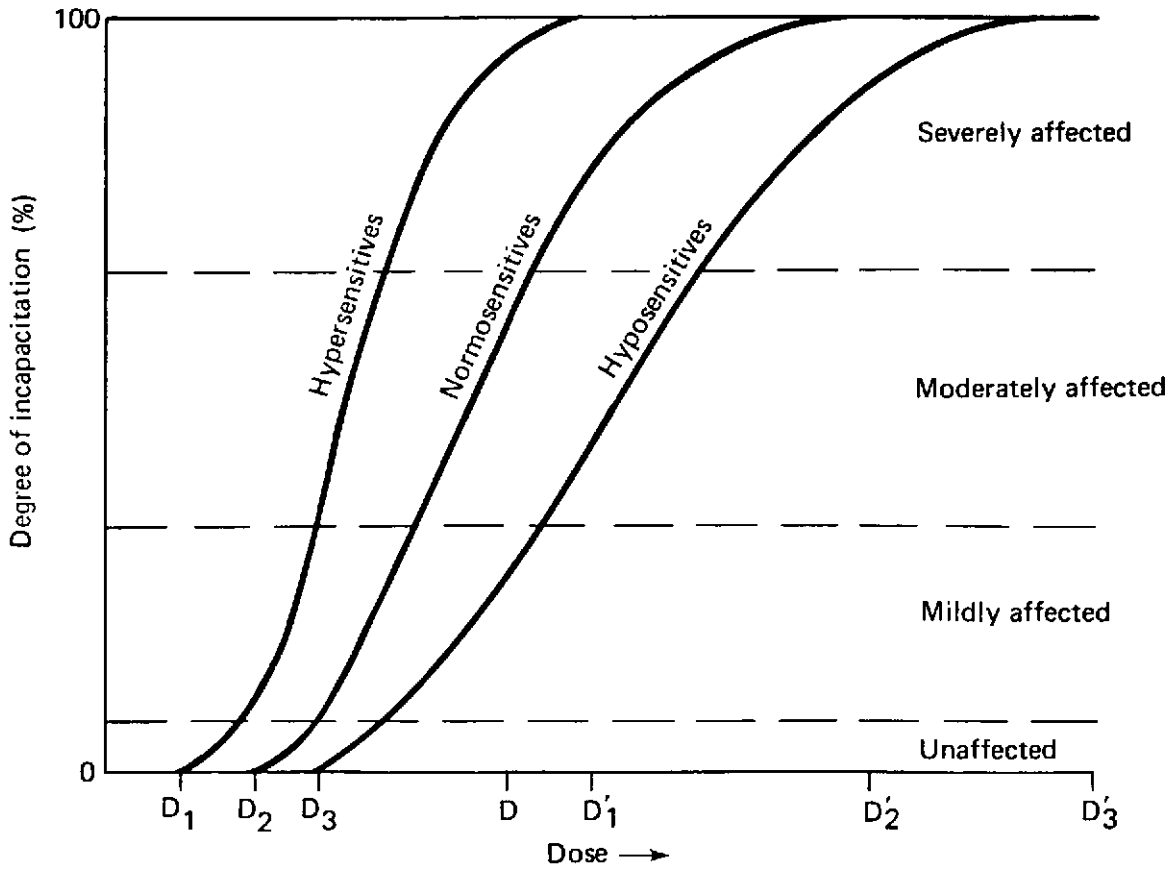


Figure 15. Individual response in initial period.

individuals in any group might well respond differently from the group norm. The curves slope more gently as sensitivity decreases, suggesting greater response variance with dose. That pattern is consistent with nonradiation types of insults [Lushbaugh, 1981].

We have divided the vertical scale representing degree of incapacitation into four regions corresponding to the population response groups: unaffected, and mildly, moderately, and severely affected. The somewhat arbitrary regional division is based on the following assumptions:

Population Response Group	Degree of Incapacitation (%)
Unaffected	0-10
Mildly affected	10-30
Moderately affected	30-60
Severely affected	60-100

Further investigation of incapacitation--perhaps applying a modified version of the Karnofsky scale* --should enable better estimates of physical and mental impairment.

Figure 16 uses the assumptions in Fig. 15 to relate individual sensitivity with population group response as a function of dose. The plots illustrate our basic presumptions: that the dose required to produce the severest symptoms and maximum incapacitation increases with decreasing individual sensitivity, and that an exposed population becomes increasingly incapacitated the higher the dose. The curves are not intended to express a quantitative assessment but to depict our modeling concept linking individual and population responses.†

---

*A scale in increments of 10 percentage points for gauging the "performance status" of persons with illnesses such as cancer.

†Appendix C presents basic algebraic relationships underlying Figs. 15 and 16 that need to be established in order to develop the model in greater detail.

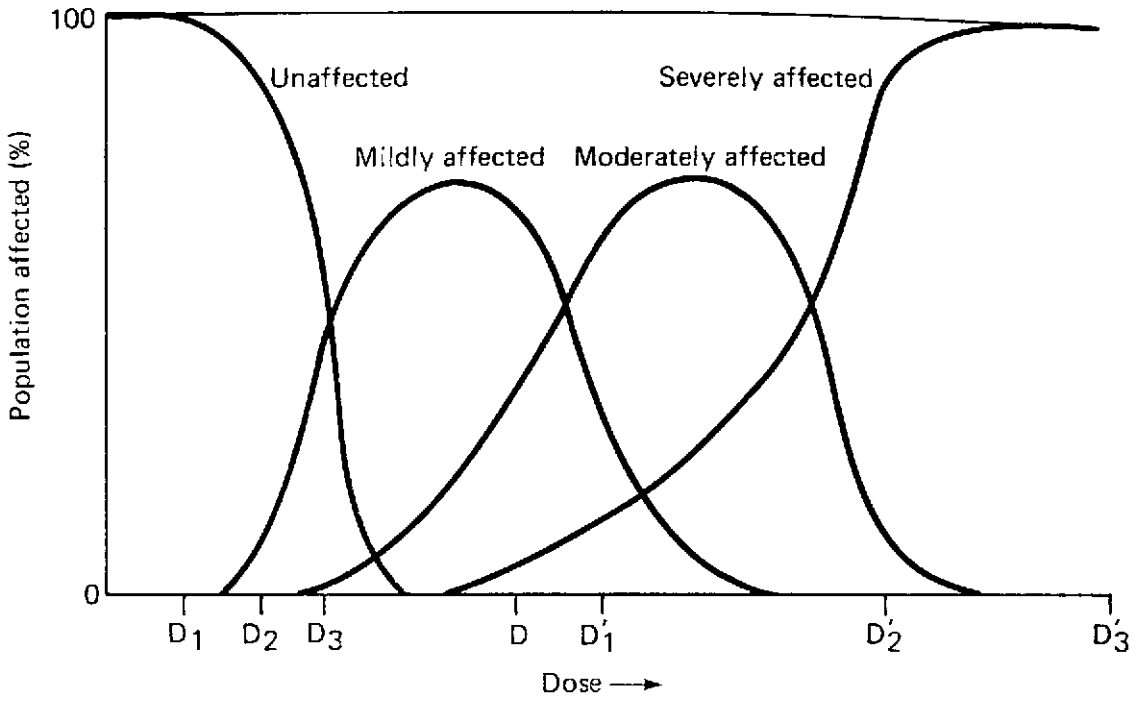


Figure 1c. Population response in initial period.

SECTION 4

CONCLUSIONS AND RECOMMENDATIONS

The limited data permit the following general conclusions:

1. Fairly specific radiation sickness symptoms can be related to absorbed dose and time after exposure for healthy adults.
2. It is reasonable to divide an exposed population into the following response groups, based on their sensitivity to radiation: hyposensitives, normosensitives, and hypersensitives.
3. It is reasonable to divide an exposed population into the following groups, based on the severity of their symptoms: unaffected, mildly affected, moderately affected, and severely affected.

We derive a hypothetical model that portrays radiation response along the dimensions of dose, time, and severity of symptoms. The model takes account of individual sensitivity to radiation and illustrates the onset and duration of both initial (prodromal) and manifest-illness periods for any given dose. We also suggest a model that links individual and population responses in the initial period as a function of dose.

To develop the models further, we need a much better understanding of the relation between radiation exposure and subsequent illness as a function of time. We need more data from noninvasive clinical studies on how therapeutic radiation affects patients' minds and bodies. Any new accident data should be carefully studied. It may be possible to make better use of data on irradiated animals, and to clarify the relation of animal behavior after irradiation to human behavior under similar conditions. It has been suggested that other animals respond more like humans in the initial postexposure period than the Rhesus

monkeys frequently used in experiments. Reexamination of the Japanese data on atomic bomb survivors may be worthwhile; the questionnaires they completed contain much detail.

Once the connection between radiation exposure and sickness is sufficiently well understood, it should be possible to make more definitive statements about how human performance will be affected by radiation. The role of such factors as psychological state, age, and training should also be considered. A study of specific military tasks and analysis of the human effort required would help correlate radiation sickness with combat performance.

Even when performance impairment is correlated with radiation exposure for *individuals*, however, questions will remain about the effectiveness of *units* in accomplishing their combat missions. For investigating how individual performance impairment influences unit effectiveness, several computerized models of military unit performance could be adapted to simulate the incapacitation effects of nuclear radiation. We recommend that such parametric studies be done, with the object of assessing the combat effectiveness of military units that have been at least partially exposed to doses greater than 100 rads. Models of small units (tank crews, artillery batteries, and the like) are needed for evaluating the speed, accuracy, and endurance with which crew members perform their assigned tasks. Then, links can be made to the activities of larger units such as battalions, divisions, and regiments.

REFERENCES

Auxier, A. J., *Ichiban: Radiation Dosimetry for the Survivors of the Bombings of Hiroshima and Nagasaki*, Technical Information Center, Energy Research and Development Agency, Report TID-27080, 1977.

Brode, H. L., "Review of Acute Radiation Health Effects for Modeling Human Response," unpublished manuscript, R & D Associates, 1977.

Brown, W. M. Court, "Symptomatic Disturbance after Single Therapeutic Dose of X-Rays," *Brit. Med. J.*, 11 April 1953, pp. 802-805.

Brucer, M. B. (comp.), *The Acute Radiation Syndrome: A Medical Report on the Y-12 Accident, June 16, 1958*, U.S. Atomic Energy Commission, Report ORINS-25, April 1959.

Cairnie, A. B., and H. A. Robitaille, *Arguments for the Greater Importance of the Prodromal Syndrome Than Incapacitation (Involving Early Transient Incapacitation) in the Consideration of Radiation Effects in Irradiated Military Personnel, Together with a Proposal to Simulate the Prodromal Effects Using Lithium Carbonate*, [Canadian] Defense Research Establishment, Ottawa, Report 836, December 1980.

Fanger, Herbert, and Clarence C. Lushbaugh, "Radiation Death from Cardiovascular Shock Following a Criticality Accident," *Arch. Path.*, Vol. 83, May 1967, pp. 446-460.

George, R. E., et al., *The Relative Effectiveness of Fission Neutrons for Miniature Pig Performance Decrement*, Armed Forces Radiobiological Research Institute, Report AFRRI-SR 71-2, March 1971.

Gerstner, Herbert B., "Acute Clinical Effects of Penetrating Nuclear Radiation," *J. Am. Med. Assn.*, Vol. 168, 27 September 1958, pp. 381-388.

-----, Oak Ridge National Laboratory, private communication, 20 August 1981.

-----, "Practical Implications of the Initial Reaction to Penetrating Ionizing Radiation," unpublished manuscript, U.S. Air Force School of Aerospace Medicine, 1970.

-----, "Reaction to Short-Term Radiation in Man," *Ann. Rev. Med.*, Vol. 11, 1960, pp. 289-302.

Gilberti, Michael V., "The 1967 Radiation Accident near Pittsburgh, Pennsylvania, and a Follow-Up Report," in K. F. Hubner and S. A. Fry (eds.), *The Medical Basis for Radiation Accident Preparedness*, Elsevier North Holland, New York, 1980.

REFERENCES (continued)

Glasstone, S., and P. J. Dolan, *The Effects of Nuclear Weapons*, 3d ed., U.S. Departments of Defense and Energy, 1977.

Gottschalk, Louis A., et al., "Total and Half Body Irradiation: Effect on Cognitive and Emotional Processes," *Arch. Gen. Psych.*, Vol. 21, November 1969, pp. 574-580.

Hemplemann, L. H., H. Lisco, and J. G. Hoffmann, "The Acute Radiation Syndrome: A Study of Nine Cases and a Review of the Problems," *Ann. Int. Med.*, Vol. 36, 1952, pp. 279-570.

Hubner, K. F., and S. A. Fry (eds.), *The Medical Basis for Radiation Accident Preparedness*, Elsevier North Holland, New York, 1980.

International Atomic Energy Agency and World Health Organization, *Diagnosis and Treatment of Acute Radiation Injury*, proceedings of a conference held in Geneva, Switzerland, 17-21 October 1960, International Documents Service, New York, 1961.

Jammet, H., et al., "Clinical and Biological Comparison of Two Acute Accidental Irradiations: Mol (1965) and Brescia (1975)," in K. F. Hubner and S. A. Fry (eds.), *The Medical Basis for Radiation Accident Preparedness*, Elsevier North Holland, New York, 1980.

Karas, Joseph S., and John B. Stanbury, "Fatal Radiation Syndrome from an Accidental Nuclear Excursion," *New Eng. J. Med.*, Vol. 272, No. 15, 15 April 1965, pp. 755-761.

Kruskal, W. H., and J. M. Tanure (eds.), "Quantal Response," *International Encyclopedia of Statistics*, Free Press, Macmillan, New York, 1978, pp. 817-824.

Langham, W. H. (ed.), *Radiobiological Factors in Manned Space Flight*, National Academy of Sciences, National Research Council Publication 1487, 1967.

Langham, W. H., P. Brooks, and D. Grahn, "Radiation Biology and Space Environmental Parameters in Manned Spacecraft Design and Operations," *Aerosp. Med.*, Vol. 2, 1965, pp. 1-55.

Laumets, E., *Time History of Biological Response to Ionizing Radiation*, U.S. Naval Radiological Defense Laboratory, Report USNRDL-TR-905, November 1965.

Levin, W. G., M. Schneider, and H. B. Gerstner, *Initial Clinical Reaction to Therapeutic Whole-Body X-Radiation--Some Civil Defense Considerations*, U.S. Air Force School of Aviation Medicine, Report 60-1, 1959.

Loewe, W. E., and E. Mendelsohn, *Revised Dose Estimates at Hiroshima and Nagasaki*, University of California Radiation Laboratory, Report UCRL-85446, October 1980.

REFERENCES (continued)

Lushbaugh, C. C., "Reflections on Some Recent Progress in Human Radiobiology," *Advances in Radiation Biology*, Vol. 3, Academic Press, New York, 1969, pp. 277-315.

-----, private communication, October 1981.

Lushbaugh, C. C., et al., *Clinical Studies of Radiation Effects in Man*, Oak Ridge Associated Universities, Radiation Research Supplement 1, 1967, pp. 398-412.

Marshall, Eliot, "New A-Bomb Studies Alter Radiation Estimates," *Science*, Vol. 212, 22 May 1981, pp. 900-903.

McDonald, C. A., J. W. Booth, H. L. Brode, S. T. Cohen, C. N. Davidson, M. R. Gustavson, C. C. Lushbaugh, C. E. Somers, Jr., B. E. Spivy, L. R. Stromberg, and J. H. Weckerling, *Report of the Defense Nuclear Agency Working Group on Nuclear Radiation Effects and Ground Combat Units*, Defense Nuclear Agency, Report DNA-4143D, September 1976.

Mendelsohn, W. E., private communication, July 1981.

Miller, Lowell S., Gilbert H. Fletcher, and Herbert B. Gerstner, "Radiobiologic Observations on Cancer Patients Treated with Whole Body X-Irradiation," *Rad. Res.*, Vol. 4, 1958, pp. 150-165.

Morgan, Ben B., and Earl E. Alluisi, "Acute Exposure to Ionizing Radiation: Potential Effects on Human Performance," unpublished manuscript, Performance Assessment Laboratory, Old Dominion University, Norfolk, Virginia, 1978.

NCRP--National Council on Radiation Protection and Measurements, *Radiological Factors Affecting Decision-Making in a Nuclear Attack*, Report 42, November 1974.

NATO Handbook on the Medical Aspects of NBC Defensive Operations, U.S. Departments of the Army, Navy, and Air Force, Report AMED P-6, August 1973.

Oughterson, Ashley W., et al., *Statistical Analysis of the Medical Effects of the Atomic Bombs*, Army Institute of Pathology, USAEC Report TID-5252, 28 February 1955.

Payne, Robert B., *Effects of Acute Radiation Exposure on Human Performance*, U.S. Air Force School of Aerospace Medicine, Aerospace Medical Division, Brooks Air Force Base, Texas, Review 3-63, 1963.

Rider, W. D., and R. Hasselback, "The Symptomatic and Hematological Disturbance Following Total Body Radiation of 300-rad Gamma-Ray Irradiation," lectures presented at McGill University, Montreal, August 1967, in *Guidelines to Radiological Health*, U.S. Public Health Service, Washington, D.C., 1968, pp. 139-144.

REFERENCES (concluded)

Saenger, Eugene L., et al., *Radiation Effects in Man: Manifestations and Therapeutic Efforts, Progress Report: May 1967 to April 1968*, University of Cincinnati, College of Medicine, [1968].

-----, *Radiation Effects in Man: Manifestations and Therapeutic Efforts*, Defense Nuclear Agency, Report DNA-2751T, October 1971.

Saenger, Eugene (ed.), *Medical Aspects of Radiation Accidents*, U.S. Atomic Energy Commission, 1963.

Shelberg, W. E., and J. C. Ulberg, *The Radiation Syndrome in Man Due to Acute, Whole-Body, External Exposure to Penetrating Ionizing Radiation--Clinical Tables*, U.S. Naval Radiological Defense Laboratory, Report USNRDL-TR-67-146, November 1967.

Thoma, George E., Jr., and Neil Wald, "The Diagnosis and Management of Accidental Radiation Injury," *J. Occ. Med.*, August 1959, pp. 421-447.

Thomas, E. D., H. L. Lochte, and J. W. Ferrebee, "Irradiation of the Entire Body and Marrow Transplantation: Some Observations and Comments," *Blood*, Vol. 14, 1959, pp. 1-23.

Vodopick, H., and G. A. Andrews, "The University of Tennessee Comparative Animal Research Laboratory Accident in 1971," in K. F. Hubner and S. A. Fry (eds.), *The Medical Basis for Radiation Accident Preparedness*, Elsevier North Holland, New York, 1980.

Wald, Neil, and George E. Thoma, Jr., *Radiation Accidents: Medical Aspects of Neutron and Gamma-Ray Exposures*, Oak Ridge National Laboratory, Report ORNL-2748, Part B, March 1961.

Wolfgang, Aaron, and John Maier, *Effects of Central Nervous System Irradiation on Human Performance, Blood Pressure and Emotional State*, Defense Nuclear Agency, Report DNA-2935F, December 1972.

Young, R. E., and G. R. Middleton, *The Effectiveness of High Energy Neutrons in Producing Behavioral Incapacitation*, Armed Forces Radiobiological Research Institute, Annual Research Report, ARP-9, 1975.

Zellmer, Robert W., "Human Ability to Perform after Acute Sublethal Radiation," *Mil. Med.*, Vol. 126, September 1961, pp. 681-687.

Appendix A

REVIEW OF JAPANESE ATOM BOMB DATA

The experience of the atom bomb survivors in Hiroshima and Nagasaki cannot be directly related to battlefield performance impairment. Nevertheless, data on exposure levels and symptoms constitute a potentially valuable source to be tapped in developing our response model.

We are primarily interested in correlating the doses that victims received with the nature and temporal occurrence of their prodromal symptoms. On the face of it, the Japanese data appear of little use to that purpose. In both Japanese cities, radiation levels attenuated greatly with distance. In each annulus of area from the blast center, symptomatic responses were not differentiated but doses differed markedly. Thus the data would not permit correlations of symptoms with dose as precise as those permitted by the therapy and accident data.

The temporal correlations possible are similarly imprecise. Data were collected from victims no sooner than 20 days after the bombings. By that time, survivors recollected the occurrence of their symptoms in terms of days, not hours and minutes, as with the therapy and accident data. For this study we needed response information in terms of hours for the first three days postexposure. (At least the Japanese data were not inconsistent with therapy and accident data: Oughterson et al. [1955] reported that in both cities about 70 percent of the exposed population vomited on the day of the bomb, and 11.5 percent vomited within the next 4 days.)

Despite those obvious limitations, we examined the Japanese data to see if they could make any contribution to our response model. This appendix describes how we evaluated the data and why we ultimately excluded them.

LEVELS OF RADIATION EXPOSURE

Figures A.1 and A.2 plot the doses to which victims were exposed at increasing distances from the blast center in Hiroshima and Nagasaki,

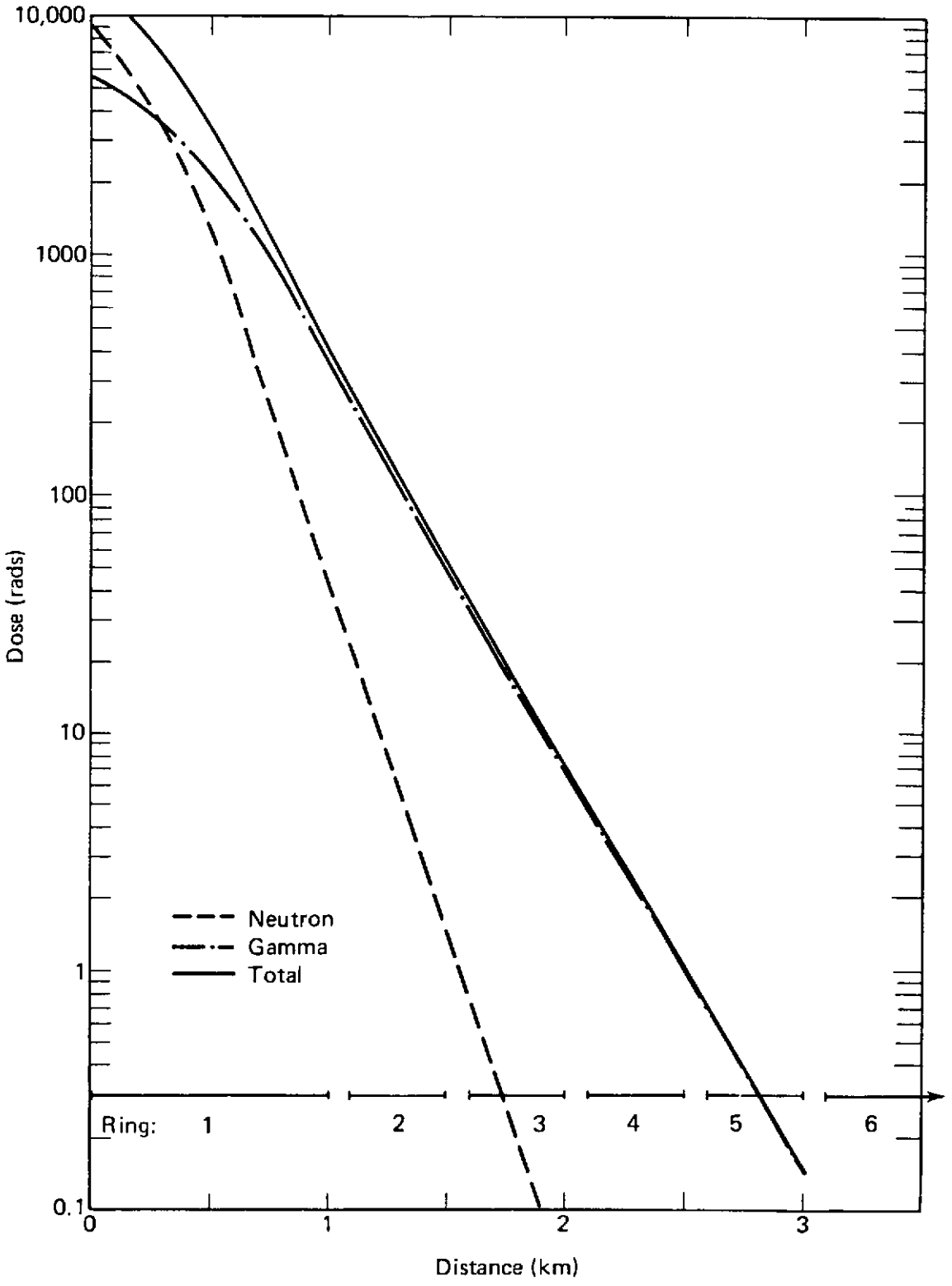


Figure A.1. Radiation dose from 15 kt Hiroshima atom bomb, by distance from blast center.

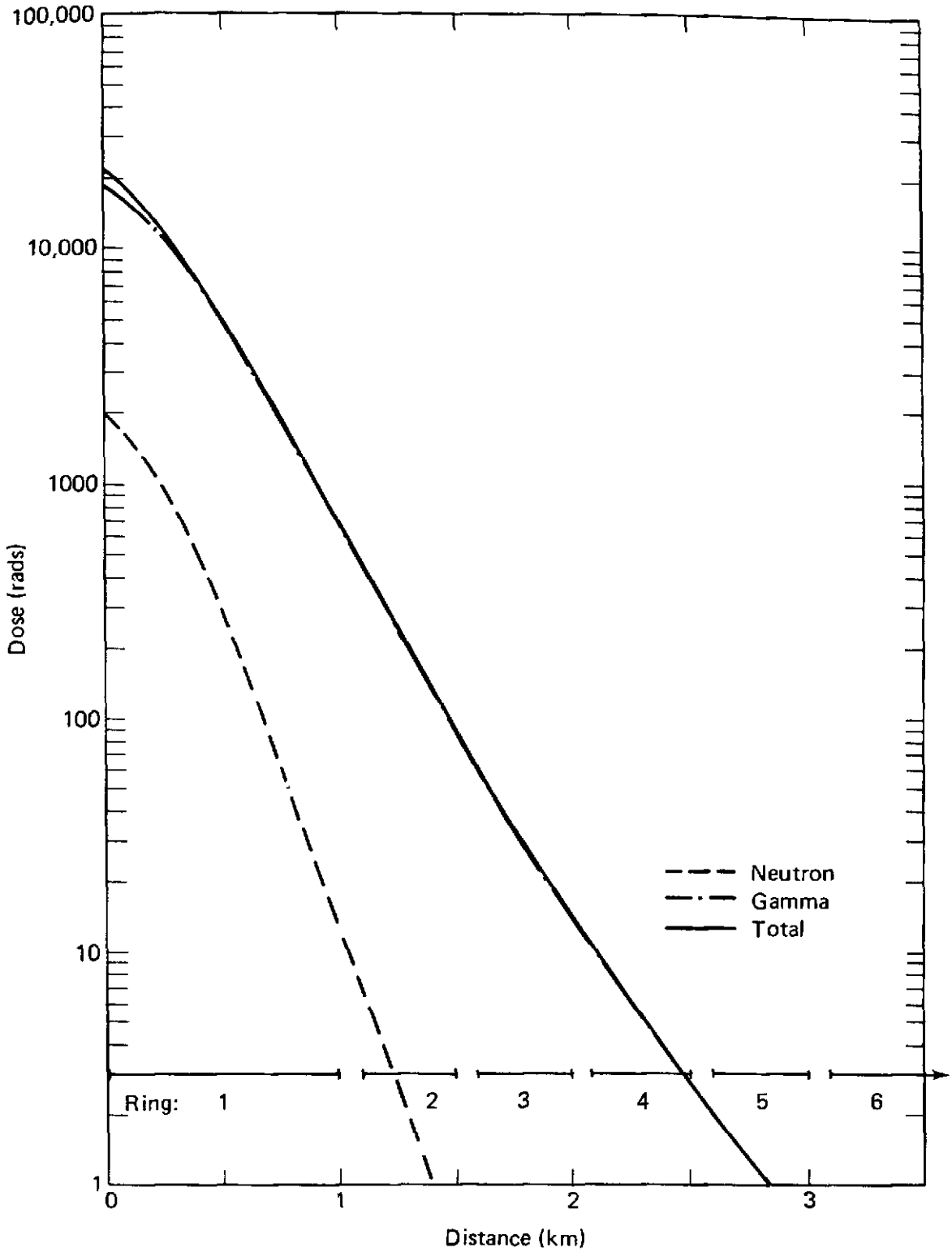


Figure A.2. Radiation dose from 22 kt Nagasaki atom bomb, by distance from blast center.

respectively. Each area is divided into rings bounded by concentric circles extending to about 3 km from the center. The graphs were drawn from revisions of the original dose estimates [Loewe and Mendelsohn, 1980; Mendelsohn, 1981]. The revised estimates begin at 600 m from ground zero; we extrapolated lesser values to the origin.

To relate dose with radiation sickness symptoms, we must first determine the average dose per ring. The following pages describe how we used the data in Figs. A.1 and A.2 to calculate those averages (the actual results are presented later in the appendix).

Average Dose per Ring--Hiroshima

For radial distances $0 \leq r \leq 1$ km, either the neutron or gamma dose relationship D(r) can be approximated by the form

$$D(r) \simeq \frac{A}{B + e^{kr}} \quad \text{rads} , \tag{A.1}$$

where the constant values are as follows:

Constant	Neutron	Gamma
A	40,984 rads	19,100 rads
B	3.657	2.351
k	6.78 km^{-1}	3.93 km^{-1}

The average neutron or gamma dose for a radial distance $0 \leq r \leq 1$ km^{-1}, i.e., ring 1, is given by

$$\langle D \rangle_1 = \frac{1}{(R_1 - R_0)} \int_{R_0}^{R_1} \frac{A\, dr}{B + e^{kr}} = \frac{A}{B} \left\{ 1 + \frac{\ln \left[\frac{\left(B + e^{kR_0} \right)}{\left(B + e^{kR_1} \right)} \right]}{k(R_1 - R_0)} \right\} . \tag{A.2}$$

Using the appropriate constant values, we obtained average neutron and gamma doses for ring 1, where $R_0 = 0$ and $R_1 = 1$ km, and added them to obtain the average total dose: $\langle D \rangle_1 = \langle D \rangle_{1,\text{gamma}} + \langle D \rangle_{1,\text{neutron}}$.

For radial distances $1 \leq r \leq 3$ km, the total (i.e., neutron and gamma combined) dose relationship D(r) may be approximated by the form

$$D(r) \simeq A_0 \, e^{-\alpha r} ,$$

where $A_0 = 20{,}650$ rads,
$\alpha = 3.94$ km^{-1}.

Average total doses for $r \geq 1$ km, i.e., rings 2 through 5, are given by

$$\langle D \rangle_{i+1} = \frac{1}{R_{i+1} - R_i} \int_{R_i}^{R_{i+1}} A_0 \, e^{-\alpha r} \, dr$$

$$= \frac{A_0}{\alpha(R_{i+1} - R_i)} \left[\exp(-\alpha R_i) - \exp(-\alpha R_{i+1}) \right] \quad \text{rads} , \qquad (A.3)$$

where i = ring index,
R_i, R_{i+1} = distances from blast center.

Average Dose per Ring--Nagasaki

For radial distances $0 \leq r \leq 1$ km, the combined neutron and gamma dose relationship D(r) may be approximated by the form

$$D(r) = \frac{A}{B + e^{kr}} \quad \text{rads} ,$$

where the constant values are A = 41,893 rads, B = 0.862, and k = 4.107 km^{-1}.

Using Eq. (A.2) with those constants, $R_0 = 0$, and $R_1 = 1$ km, we obtained the total average dose for ring 1.

For radial distances $r \geq 1$ km, the total (combined neutron and gamma) dose relationship is given by

$$D(r) = A_i \exp(-\alpha_i r) \quad \text{rads} ,$$

where the following values obtain:

Ring, i	Distance (km)	A_i(rads)	α_i (km^{-1})
2	$1.5 \geq r \geq 1$	38,819	4.045
3	$2 \geq r \geq 1.5$	23,892	3.721
4	$2.5 \geq r \geq 2$	8,750	3.219
5	$3 \geq r \geq 2.5$	4,377	2.942
6	$3.5 \geq r \geq 3$	4,377	2.942

Average total doses for rings 2 through 6 are given by

$$\langle D \rangle_{i+1} = \frac{A_i}{\alpha_i (R_{i+1} - R_i)} \left[\exp(-\alpha_i R_i) - \exp(-\alpha_i R_{i+1}) \right] ,$$

where i = ring index,

R_i, R_{i+1} = distances from blast center

PRODROMAL SYMPTOMS

We used the per-ring average doses to classify by distance the incidence of nausea and vomiting as representative symptoms of prodromal radiation sickness. Table A.1 presents the results. The symptomatic data pertain to day 1 but were gathered by American physicians from survivors 20 days after the bombings [Oughterson et al., 1955]. The number of cases in each ring ensures that the responding percentages are reasonably precise. The pattern of vomiting here appears consistent with that observed among therapy patients and accident victims.

Figure A.3 displays the incidence of symptoms by dose, plotting the data in Table A.1 and adding data from therapy patients and accident

Table A.1. Nausea and vomiting among survivors of Hiroshima and Nagasaki bombings.

Ring	Distance from Blast Center (km)	Average Dose (rads)	Total Population	Vomiting		Nausea	
				Number Affected	Percent of Population	Number Affected	Percent of Population
Hiroshima							
1	0-1	4945	749	264	35.2	269	35.9
2	1.1-1.5	175	1125	290	25.8	321	28.5
3	1.6-2.0	25	1824	178	9.8	214	11.7
4	2.1-2.5	3.5	1450	106	7.3	148	10.8
5	2.6-3.0	.47	700	40	5.7	53	7.6
Nagasaki							
1	0-1	7190	789	213	27.0	223	28.5
2	1.1-1.5	292	1882	508	27.0	537	28.5
3	1.6-2.0	41	1034	163	15.8	164	15.9
4	2.1-2.5	7	672	62	9.2	73	10.9
5	2.6-3.0	1.5	644	44	6.8	54	8.4
6	3.1-4.0	.21	1141	55	4.8	58	5.1

victims for comparison [Langham (ed.), 1967]. The Langham data derive from probit analyses, assuming either a normal or log-normal distribution.* At the low-dose end, Langham found a much better fit when a log-normal distribution was assumed; at the high-dose end the fit was better assuming a normal distribution. In Fig. A.3, accordingly, the Langham data are represented by two curves. The curve between 10 and 100 rads is based on a log-normal distribution, and the curve beginning at 40 rads is based on a normal distribution. The values at 70 rads in both curves are essentially equivalent.

The incidence of nausea and vomiting as a function of average dose was quite similar in the two Japanese cities. This suggests that despite the likely differences in radiation characteristics, relative biological effectiveness (RBE) in the two sites was similar for prodromal symptoms.

*Lushbaugh et al. [1967] obtained similar data from probit analyses.

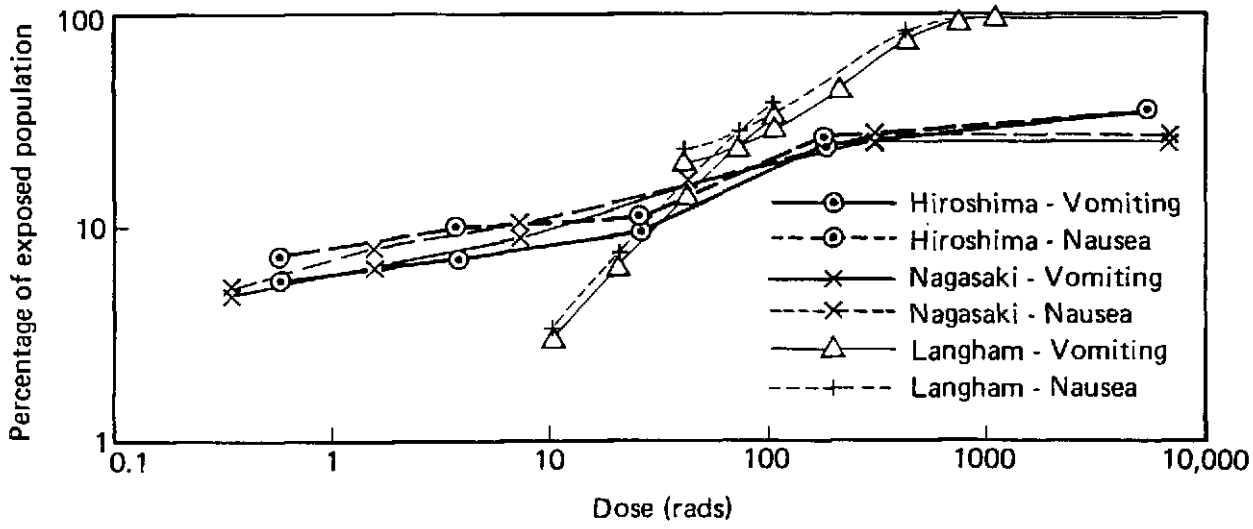


Figure A.3. Nausea and vomiting in atom bomb survivors (Hiroshima, Nagasaki) versus therapy patients and accident victims (Langham).

But the Japanese data differ markedly from the Langham data. At higher doses (more than 100 rads), the therapy and accident data suggest a more severe response than do the Japanese data; at lower doses the therapy and accident data suggest a lighter response. Since our investigation focuses on doses over 100 rads, how might we account for the differences in the two data sources at the higher doses?

One could hypothesize that the Japanese response appears lighter because most victims in rings 1 and 2 (blast center to 1.5 km) were exposed to the lowest doses recorded for the ring. Such an occurrence would lower the averages on which Fig. A.3 is based. However, Fig. A.1 suggests that for Hiroshima the lowest dose in ring 1 was ~400 rads, and that in ring 2 was ~50 rads. In Nagasaki, Fig. A.2, the corresponding lower limits were ~650 rads (ring 1) and ~90 rads (ring 2). Those doses are high enough to expect the Japanese responses to be much closer to those shown in the therapy and accident data.

Another possible explanation might be that many Japanese victims were shielded from the full effects of the free-in-air doses shown in Figs. A.1 and A.2. However, Oughterson et al. [1955] report that only 21 out of 1874 persons in Hiroshima, rings 1 and 2, were in bomb shelters or tunnels (in Nagasaki, 145 out of 2671). The rest in both cities were either outdoors or in Japanese types of structure, which afford relatively poor radiation shielding [Auxier, 1977].

It might also be postulated that those who gathered the Japanese data were dealing with a biased sample. Persons surviving after 20 days could represent the "healthier" or hyposensitive portion of the population; the majority might have been too sick to give an account of their illness and were overlooked in the study. The material reviewed offers no means of investigating that hypothesis.

The uncertainties surrounding the discrepancies manifested in Fig. A.3, plus more fundamental questions recently raised about the accuracy of the radiation levels particularly in Hiroshima [Marshall, 1981] persuaded us to exclude the Japanese atom bomb data from consideration in our Sec. 3 response model.

Appendix B

SIDE EFFECTS OF TOTAL-BODY IRRADIATION IN THERAPY PATIENTS

H. Rodney Withers
Department of Radiation Oncology
Center for Health Sciences
University of California at Los Angeles

Physicians and medical researchers have been less interested in the side effects of therapeutic total-body irradiation (TBI) than in its effects on the disease itself. As a result, there is a dearth of published data on the manifestations and interpretation of acute radiotoxicity. To improve our understanding of symptomatic responses for the present investigation, I have gathered what is known about the subject from published sources and from my own and colleagues' observations.

In the past decade at least 1500 patients have been treated with TBI, mainly for leukemia but also for aplastic anemia and other diseases. A substantial number of patients have been treated with half-body irradiation, where either one-half of the body is irradiated or both halves are irradiated sequentially, with an interval of 6 to 8 weeks between treatments to allow for repopulation of irradiated bone marrow from the other half of the body. Some patients with chronic lymphatic leukemia or lymphoma have been treated with multiple small dose increments (e.g., 10 rads) adding to low total doses (e.g., 120 to 200 rads). Finally, a group of patients with mycosis fungoides have been treated over their total skin surface using electrons that penetrate only about 1 cm.

IRRADIATION METHODS AND DOSIMETRY

The dosimetry has not always been optimal, but most specified doses have probably been accurate to ±10 percent. The doses have usually been specified at mid-body; therefore, near the body surface and in thinner regions such as the head, neck, and limbs doses have been higher by up to 15 percent. The radiation has always been in the million-electron-volt range, usually from a cobalt 60 source but sometimes using linear accelerators producing up to 25 MeV.

The radiation methods can be grouped as follows:

1. TBI, single exposure, low dose rate: 4 to 12 rads/min, total dose, 800 to 1200 rads.
2. TBI, single exposure, high dose rate: 20 to 25 rads/min, total dose, 750 rads.
3. TBI, up to 6 or 8 exposures, high dose rate: 200 rads/day, several hours apart, total dose, 1200 to 1600 rads.
4. TBI, multiple small exposures, high dose rate: 10 rad exposure, total dose, 120 to 200 rads.
5. TBI of skin using 2.5 MeV electrons: fractional dose, ≤200 rads, total dose, 800 to 4000 rads.
6. Half-body radiation or sequential half-body radiation at high dose rate using total doses of 600 to 1000 rads.

The remainder of this appendix focuses on responses to methods 1 through 3, which most closely resemble high-dose-rate single exposures of 750 to 1000 rads.

FACTORS MODIFYING IRRADIATION RESPONSE (750 to 1000 RAD DOSE EQUIVALENTS)

All patients had a life-threatening disease although some were in reasonably good condition; many were young.

Patients were not stressed. Most were treated with extreme care, and many were placed in "life islands" where conditions were maximally favorable to asepsis. To counter the ill effects of radiation exposure, all patients were given sedatives, antiemetics, steroids, and intravenous fluids before their treatments.

Before undergoing TBI, most patients had received large doses of chemotherapy. That treatment could have contributed to the severity of the postirradiation skin and mucosal reactions and perhaps to sequelae in other organs. The depletion of normal bone marrow cells resulting from chemotherapy probably did not significantly alter patients' initial radiation responses such as nausea and vomiting. (Longer-term hemopoietic effects of radiation exposure would have been altered,

however, because all patients undergoing TBI received bone marrow grafts after irradiation.)

ACUTE SEQUELAE (750 TO 1000 RAD DOSE EQUIVALENTS)

Shortly after exposure, most patients experienced *nausea, emesis, chills, and fever.* Those symptoms usually subsided within about 10 hr and disappeared within 24 hr except for nausea and anorexia, which could persist for days. Emesis was aggravated by movement and often occurred with little warning.

In the first few hours after exposure, some patients experienced *decreased blood pressure and increased pulse rate* due to circulatory hypovolemia. There were reports of acute myocardial insufficiency and death in patients with a history of myocardial disease.

A painful mumps-like *swelling of the parotid gland* developed within a few hours of exposure. The pain usually subsided within 2 days; the swelling sometimes persisted for several days. Xerostomia (dry mouth) sometimes lasted a week or more. During that time the saliva was reduced in volume, was thicker, and felt ropey. A metallic taste could persist as long as the mouth remained dry. Reduced salivary secretion added to patients' disinterest in food.

About 10 percent of the patients developed *diarrhea* soon after irradiation. More developed diarrhea 1 to 7 days after exposure.

The *oropharyngeal mucosae* became reddened and sore 1 to 3 days after exposure and subsequently ulcerated. The condition took about 3 weeks to disappear. About 75 percent of the patients developed *oral infections*, owing not only to the ulcerated mucosae but also to leukocytopenia and immunosuppression. These infections became apparent as soon as 3 days after irradiation. The most common were fungal (thrush), but bacterial and herpes infections were also seen.

A generalized *erythema* appeared as soon as 1 day after irradiation though usually later. It persisted for as long as 2 weeks and was sometimes associated with perineal irritation and itchiness. Beginning 7 to 10 days after exposure there was a temporary incomplete *loss of hair.* Sweating appeared to decrease in some patients, but that phenomenon has not been adequately investigated.

Bone marrow suppression was indicated by increased susceptibility to infections and bleeding (e.g., of the gums) several days after exposure. If the patient had a preexisting infection, however, TBI was usually fatal, sometimes during the first postexposure week. Bone marrow grafts did not mitigate that result.

RESPONSE TO HIGHER SKIN DOSES

When doses of electrons equivalent to a single exposure of 1000 to 2000 rads were given to the skin, the incidence and severity of responses described above increased. The most important seemed to be decreased sweating associated with a generalized burning sensation and a low tolerance to exercise or heat with consequent high risk of hyperthermia. That phenomenon has been little investigated in patients treated with electrons that penetrated about 1 cm below the skin. In X- or gamma-ray treatments, the energy of the beams was high enough to "spare" the skin. The electron treatments, with doses that produced only partial epilation and decreased sweating, also resulted in a loss of fingernails; how soon after exposure was not indicated. (In current skin treatments with electrons, fingernails are protected by lead shields.)

PROBLEMS IN ASSESSING SIDE EFFECTS

Little Data on Effects of TBI at Less Than 750 Rads

Very few patients (e.g., about 20) received 300 rad doses of TBI; data on the side effects they experienced have not been published. Continuing attempts to optimize and individualize dose regimens may permit a better assessment of dose-response relationships.

Multiple Variables

The premedication and management of patients receiving TBI is improving. Acute side effects have been alleviated by premedication with antiemetics, steroids, and intravenous fluids. Infections have been reduced by preradiation decontamination and by not treating patients

having evidence of infection. It would be useful to try to reconstruct what the results of treatment would have been without such sophisticated measures for reducing morbidity.

Importance of Inhibition of Sweating Unknown

*Inhibition of sweating is not a problem in usual clinical radio-*therapy because only small surface areas are irradiated. It could be lethal if large single doses are delivered from sources that do not spare the skin. Sweating was studied in patients receiving a series of small doses over a 6 week period. It is difficult to estimate the single-dose equivalent from the published data, but it is less than 2000 rads and perhaps about 1500 rads.

PROSPECTIVE STUDIES

In the effort to pursue a careful, comprehensive, and quantitative examination of TBI effects on normal tissue, we need to know more about postexposure fatigability and sweating patterns. Only one report has mentioned fatigability. Twenty-seven patients were treated with only 10 rads per day, three or five times per week, for total doses of 120 to 200 rads. Even at such low doses, two patients complained early of fatigability, and "most" complained of it 2 weeks to 4 months after the completion of treatment. Evidence of fatigability is not usually sought in patients treated with high doses of TBI because they are sicker and have more restricted mobility than patients receiving small fractional doses. But fatigability would be a significant factor in considering radiation effects in otherwise healthy adults. Sweating patterns could be investigated in patients receiving high doses of radiation to the skin, as for skin or breast cancer.

Appendix C

FORMULAS UNDERLYING THE RESPONSE MODEL

At the end of Sec. 3, we set forth the basic concepts of a model linking individual and population responses in the initial period as a function of dose. The model was illustrated in Figs. 15 and 16. This appendix presents algebraic formulas that explain how values for the curves in Figs. 15 and 16 could be derived. If these functional relationships can be established, it will be possible to add the time dimension, now omitted, to Figs. 15 and 16.

We assume that the following are known:

x_1, percentage of hypersensitives in population (~15 to 25)
x_2, percentage of normosensitives in population (~50 to 70)
x_3, percentage of hyposensitives in population (~15 to 25)
D_1, threshold response dose for hypersensitives (100 rads)
D_2, threshold response dose for normosensitives (150 rads)
D_3, threshold response dose for hyposensitives (200 rads).

We also presume the following:

y_a, maximum incapacitation for unaffected (10 percent)
y_b, maximum incapacitation for mildly affected (30 percent)
y_c, maximum incapacitation for moderately affected (60 percent
y_d, maximum incapacitation for severely affected (100 percent)
D_1', dose producing maximum incapacitation in hypersensitives (few hundred rads)
D_2', dose producing maximum incapacitation in normosensitives (several hundred rads)
D_3', dose producing maximum incapacitation in hyposensitives (few thousand rads).

We define the portion of the population by symptom severity as

f_{un}, percentage unaffected
f_{mild}, percentage mildly affected
f_{mod}, percentage moderately affected
f_{sev}, percentage severely affected.

We require that

$$f_{un} + f_{mild} + f_{mod} + f_{sev} = x_1 + x_2 + x_3 = 100 \ . \qquad (C.1)$$

The two response-group classifications can be linked by considering an arbitrary dose designated D. Thus, the percentage of hypersensitives that are severely affected is

$$f_{1,sev} = \left(\frac{y_{1,sev} - y_c}{y_d - y_c} \right) x_1 \ , \qquad y_c \leq y_{1,sev} \leq y_d \ . \qquad (C.2)$$

Since at D the cumulative response function $y_{1,sev}$ exists somewhere between the upper limits of the moderately and severely affected boundaries, for simplicity we assign all other hypersensitives to the next lower severity category. The percentage of hypersensitives that are moderately affected is then

$$f_{1,mod} = \left(1 - \frac{y_{1,sev} - y_c}{y_d - y_c} \right) x_1 \ . \qquad (C.3)$$

Similarly, the percentage of normosensitives that are moderately affected is

$$f_{2,mod} = \left(\frac{y_{2,mod} - y_b}{y_c - y_b} \right) x_2 \ , \qquad y_b \leq y_{2,mod} \leq y_c \ , \qquad (C.4)$$

and the percentage that are mildly affected is

$$f_{2,\text{mild}} = \left(1 - \frac{y_{2,\text{mod}} - y_b}{y_c - y_b}\right) x_2 \ . \qquad \text{(C.5)}$$

The percentage of hyposensitives that are mildly affected is

$$f_{3,\text{mild}} = \left(\frac{y_{3,\text{mod}} - y_a}{y_b - y_a}\right) x_3 \ , \qquad y_a \le y_{3,\text{mod}} \le y_b \ . \qquad \text{(C.6)}$$

Then at dose D the population response distribution (Fig. 16) is

$$\text{Severely affected:} \quad f_{\text{sev}} = f_{1,\text{sev}} \ , \qquad \text{(C.7)}$$

$$\text{Moderately affected:} \quad f_{\text{mod}} = f_{1,\text{mod}} + f_{2,\text{mod}} \ , \qquad \text{(C.8)}$$

$$\text{Mildly affected:} \quad f_{\text{mild}} = f_{2,\text{mild}} + f_{3,\text{mild}} \ , \qquad \text{(C.9)}$$

$$\text{Unaffected:} \quad f_{\text{un}} = 100 - (f_{\text{sev}} + f_{\text{mod}} + f_{\text{mild}}) \ . \qquad \text{(C.10)}$$

Some boundary relationships can now be readily established. In addition to requiring Eq. (C.1) above, we set the boundary conditions listed below. Numbers 1 and 2 are external, 3 through 6 are internal.

$$1. \quad \text{At } D_1: \quad f_{\text{un}} = 100, \ f_{\text{mild}} = f_{\text{mod}} = f_{\text{sev}} = 0 \ . \qquad \text{(C.11)}$$

$$2. \quad \text{At } D_3': \quad f_{\text{sev}} = x_1 + x_2 + x_3 = 100 \ , \qquad \text{(C.12)}$$

$$f_{\text{un}} = f_{\text{mild}} = f_{\text{mod}} = 0 \ . \qquad \text{(C.13)}$$

3. For $D \geq D_2'$: $f_{un} = f_{mild} = 0$, (C.14)

$$f_{sev} = x_1 + x_2 + f_{3,sev} , \tag{C.15}$$

$$f_{mod} = 100 - f_{sev} , \tag{C.16}$$

where $f_{3,sev} = \left(\frac{y_{3,sev} - y_c}{y_d - y_c} \right) x_3$,

$$y_c \leq y_{3,sev} \leq y_d . \tag{C.17}$$

4. At D_1': $f_{sev} = x_1 + f_{2,sev}$, (C.18)

$$f_{mod} = f_{2,mod} + f_{3,mod} , \tag{C.19}$$

$$f_{mild} = f_{3,mild} , \tag{C.20}$$

$$f_{un} = 0 , \tag{C.21}$$

where $f_{2,sev} = \left(\frac{y_{2,sev} - y_c}{y_d - y_c} \right) x_2$,

$$y_c \leq y_{2,sev} \leq y_d , \tag{C.22}$$

$$f_{2,mod} = \left(1 - \frac{y_{2,sev} - y_c}{y_d - y_c} \right) x_2 , \tag{C.23}$$

$$f_{3,mod} = \left(\frac{y_{3,mod} - y_b}{y_c - y_b} \right) x_3 ,$$

$$y_b \leq y_{3,mod} \leq y_c , \tag{C.24}$$

$$f_{3,mild} = \left(1 - \frac{y_{3,mod} - y_b}{y_c - y_b} \right) x_3 . \tag{C.25}$$

5. At D_2: $f_{sev} = f_{mod} = 0$, (C.26)

$$f_{mild} = f_{1,mild} \text{ ,} \quad \text{(C.27)}$$

$$f_{un} = 100 - (f_{mild} + f_{mod} + f_{sev}) \text{ ,} \quad \text{(C.28)}$$

where $f_{1,mild} = \left(\frac{y_{1,mild} - y_a}{y_b - y_a} \right) x_1$

$$y_a \leq y_{1,mild} \leq y_b \text{ .} \quad \text{(C.29)}$$

6. At D_3: $f_{mild} = f_{1,mild}$, (C.30)

$$f_{sev} = f_{mod} = 0 \text{ ,} \quad \text{(C.31)}$$

$$f_{un} = 100 - (f_{mild} + f_{mod} + f_{sev}) \text{ ,} \quad \text{(C.32)}$$

where $f_{1,mild} = \left(\frac{y_{1,mild} - y_a}{y_b - y_a} \right) x_1$,

$$y_a \leq y_{1,mild} \leq y_b \text{ .} \quad \text{(C.33)}$$